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FOR HAY FEVER

Extensive clinical experience of physicians in all sections of the United States has demonstrated during the past thirteen years that hay-fever can be prevented or alleviated with Pollen Antigens (*Lederle*).

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* { Illustrated booklet with complete information
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"Imitation yeast"
fails in test but
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in every case

THAT "psychic influences come into play to a great extent in the regulation of bowel movements" is held by two well-known scientists to be "common knowledge." Both these men are connected with the department of physiological chemistry of one of the most prominent medical colleges and hospitals in the East.

It is the above consideration, they assert, which prompted them to undertake a careful study to ascertain whether such psychic influences play any part in the laxative action of fresh yeast.

To put the matter in their own words, they set themselves the following question, "Is yeast a more efficient treatment for constipation than some substance which would look and taste like yeast?"

The first step was to prepare an "imitation yeast." To do this, 70% cream cheese and 30% tapioca starch by weight were mixed and wrapped in cakes to resemble an ordinary compressed yeast cake, and the subjects of the experiment were led to believe that this was a new strain of yeast.

Then, to a group of 15 subjects a dosage of 3 cakes of this imitation yeast was administered daily, in addition to their usual diet, while to a second group of 25

subjects, a daily dosage of 3 cakes of fresh yeast was administered. All 41 of the subjects were normal adults, following their usual occupations. The entire experiment, including control periods, continued for over a month.

In summarizing the results, the investigators state, "That the live yeast in a dosage of 3 cakes per day improved the condition of every individual who had any degree of constipation." (*Italics ours.*)

The imitation yeast, on the other hand, seemed to have precisely the opposite, i. e., a constipating effect, on several of the subjects, while on the majority it had no effect whatsoever.

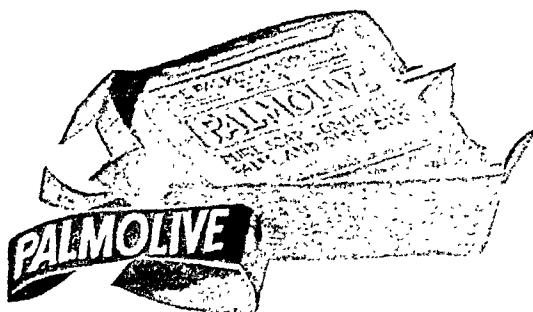
In this experiment, then, it is strikingly demonstrated that the beneficial results obtained by the ingestion of fresh yeast in constipation are independent of psychic influences.

Fresh yeast, conclude the investigators in their report, "tends to soften the fecal masses . . . It is quite effective in cases of mild or chronic constipation."

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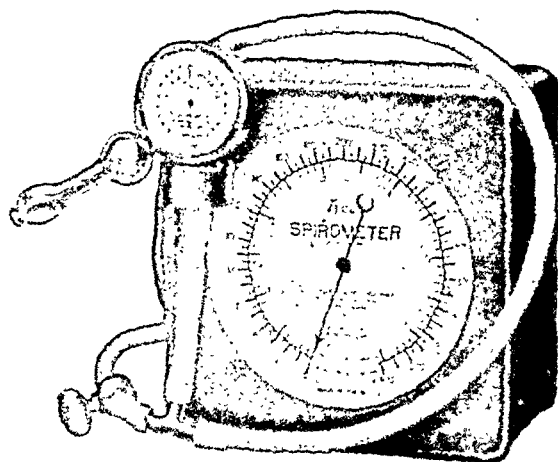
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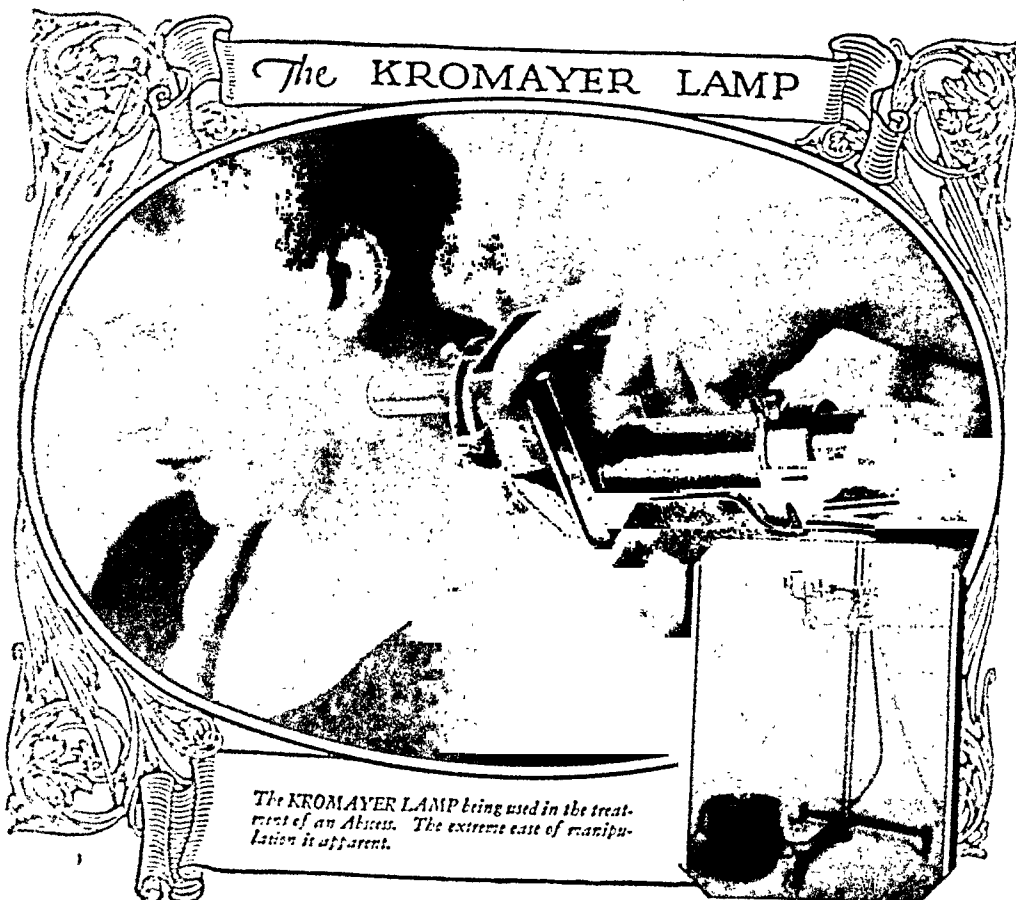
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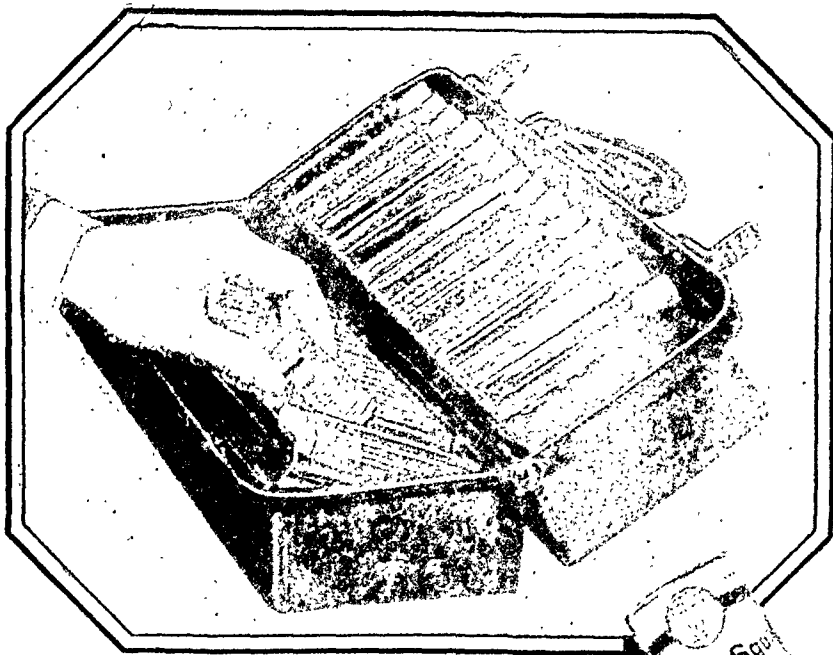
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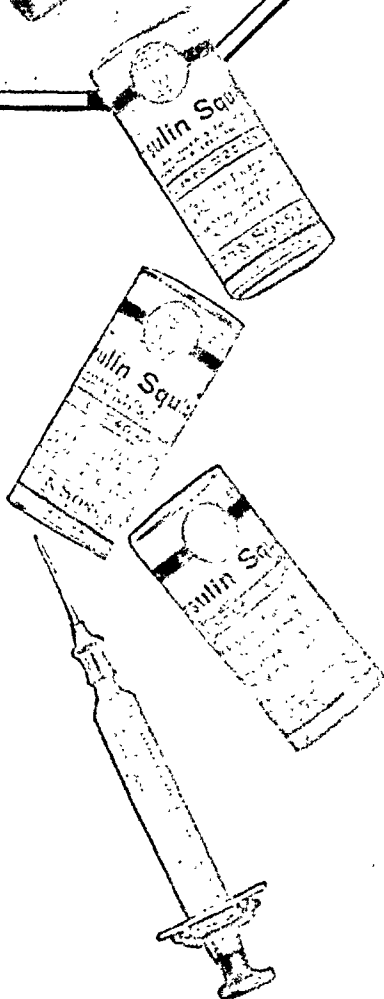
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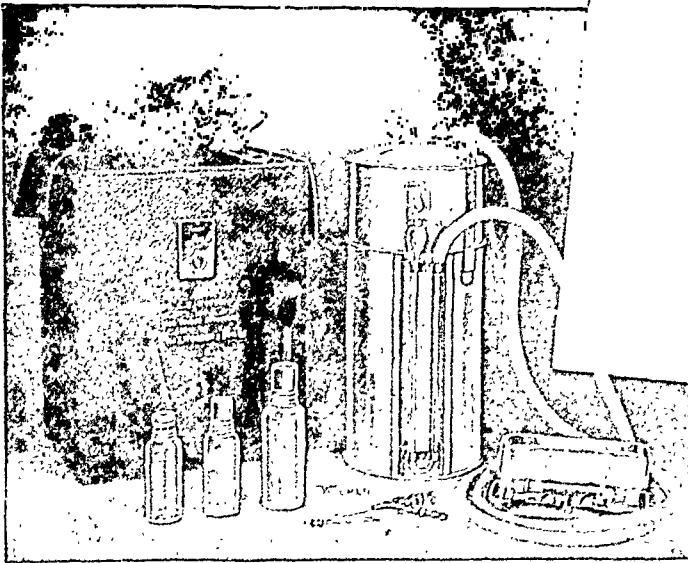
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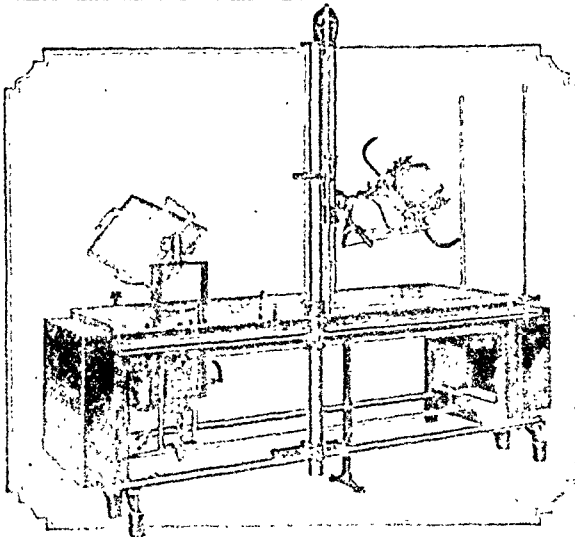
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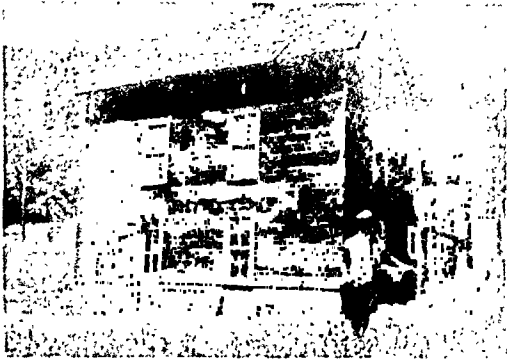
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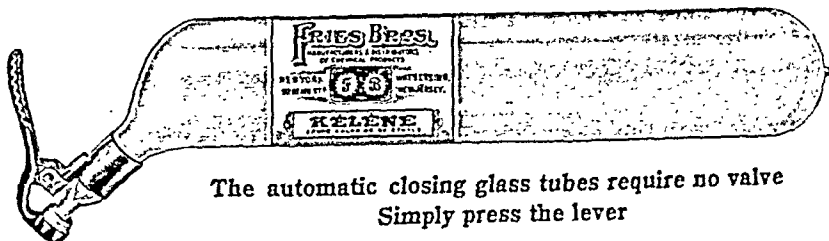
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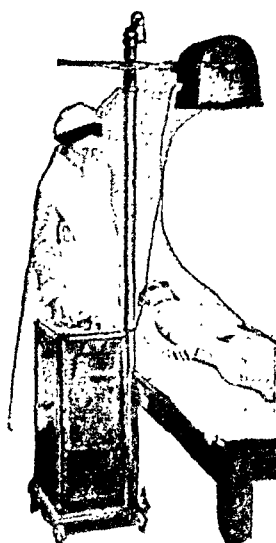
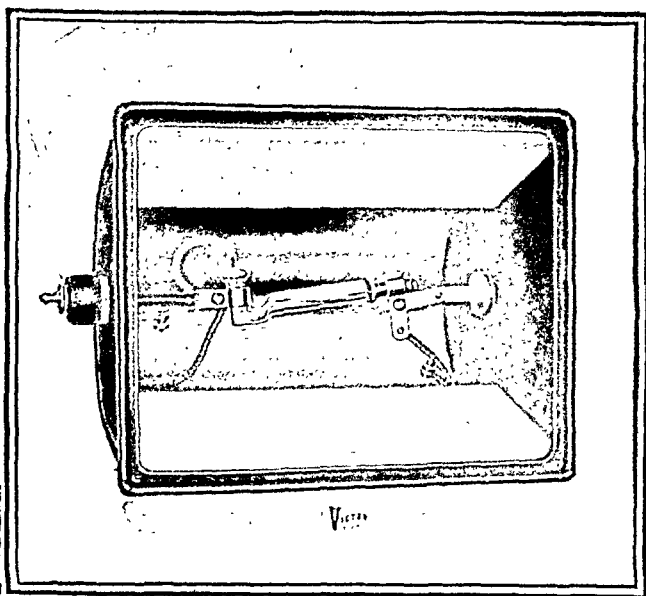


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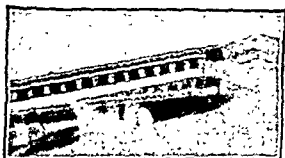
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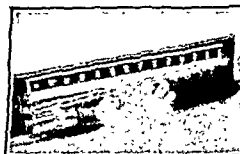
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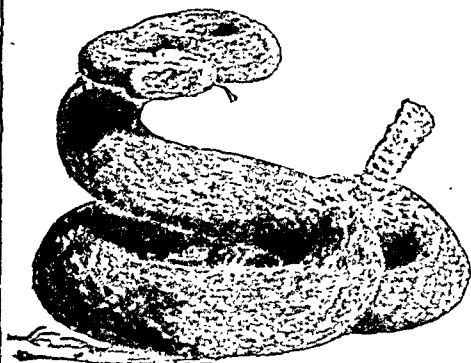


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ALLEN J. SMITH

ALLEN J. SMITH.

Allen J. Smith, A.M., M.D., Sc.D.

Born, 1863.

Gettysburg College, A.B., 1883; A.M., 1886; Sc.D., 1910.

University of Pennsylvania, M.D., 1886.

Magill University, LL.D., 1911.

Assistant Demonstrator of Pathology, University of Pennsylvania, 1887-1891.

Professor of Pathology, University of Texas, 1891-1903 (Dean of Faculty for ten years).

Professor of Pathology and Comparative Pathology and Director of Courses in Tropical Medicine, 1911 (Dean of Medical Faculty; 1909-1912; Acting Dean, 1917-1918), University of Pennsylvania.

Lieutenant-Colonel, Medical Department, U. S. Reserve Corps (active service, June, 1918 to April, 1919).

Died, 1926.

Class Book on Bacteriology. Translations of Kitt's *Comparative General Pathology* and von Fürth's *Problems of Physiological and Pathological Chemistry of Metabolism.*

Medical News prize. Anatomic prize.

Sections in various textbooks upon legal medicine in various modes of death; animal parasites and the principles of immunity; journal articles upon a variety of subjects in pathologic anatomy, parasitology and tropical affections.

Discovery of *Bacillus cœruleus* (one year after graduation from medical school).

Establishment of hookworm disease as endemic in the United States.

Production of evidence implicating bedbugs as conveyors of leprosy infection and of ticks as harboring larvæ of certain filarial worms.

Incrimination of the mouth ameba as a contributing cause of pyorrhea alveolaris and suggesting emetin as a helpful treatment.

In 1895, Allen J. Smith first observed, and recognized as such, hookworm ova recovered from the feces of the common closet of the Medical Department of the University of Texas. Search for the individual host or hosts was unavailing.

In 1901, he found similar ova in the stools of a patient in St. Mary's infirmary, and, following the administration of thymol and

salts recovered more than 100 parasites from the dejecta. The ova from this patient were demonstrated to the medical students who, working over some presumably normal fecal matter taken from the common closet of the school, found simular ova in large numbers. Search for the hosts was again fruitless.

A month later the finding of a distinct eosinophilia in the blood of 2 students exhibiting malarial symptoms suggested an examination of the stools, from which were recovered in both cases hookworm ova. Shortly thereafter Dr. Smith examined the feces of 86 students, coming, in the main from widely different parts of the state of Texas. Eight exhibited hookworm infection.

Dr. Smith's work upon hookworm disease was fundamental and conclusive of the proposition that this affection was endemic in this country. He later realized the portent of his observations and lived to see the inestimable benefits accruing therefrom to our southern states and to many tropical and subtropical lands.

Called in 1891 to the Chair of Pathology, Microscopy and Bacteriology at the University of Texas, just taken over by the state, Dr. Smith found this institution representing little more than an earnest effort toward medical education. He left it in 1903, a school of high standing, to accept the Professorship of Pathology in the University of Pennsylvania.

In Texas he was his own janitor until a slight increase in his budget enabled him to secure at a low price a temperamental leper, who served well for some years until his physical infirmity was recognized by an overbright student and reported to the daily press. As for the leper's mental obliquity, distrained of his liberty at St. Mary's Hospital, he flatly refused that autopsy, the hope for which may have been a contributing cause of his janitorial appointment.

In Texas Dr. Smith taught histology, embryology, inorganic chemistry and lectured on mental and nervous diseases. At his request his title was changed to Professor of Pathology.

Dr. Randall writes that, during his residence in Texas, there came to Dr. Smith a call to the pathological professorship of one of the largest and strongest medical schools in this country; with the assurance of an adequate budget, abundant medical and surgical material and a salary, a thousand dollars more than the one he was receiving.

The students called a mass meeting, raised a thousand dollars and presented this to Dr. Smith, with an earnest petition that he stay with them. Both check and the call of the larger institution were refused.

As Dean of the School, ably abetted by such men as Kislén Thompson and Randall, he inspired that confidence, respect and personal regard which insured both individual and legislative financial support.

He held that the first duty of a teaching department is to teach and carried this doctrine to its ultimate conclusion; using for this purpose the rich autopsy and operative material afforded by hospitals of more than 2000 beds. He particularly stressed the relation borne by pathologic anatomy to disturbances of function and the symptoms resulting therefrom. He and his class habitually became so enthralled by his and their study and description of abnormal findings in a given organ, and symptoms which must have resulted therefrom that, forgetful of other subjects and professors, they would continue their discussion long past the appointed hour. Disarmingly contrite when protests were made, when he again met his class he and it, each stimulating the other, became amnesic to aught but pathology.

He rejected, and with contumely, the offer of one whose hour followed his, to supply an alarm clock which, harshly ringing at the appointed time, should rapidly release a mephitic vapor.

Even his final examination was a teaching one.

A big, sturdy, large-framed, broad-shouldered, powerful man, pale rather than red, clear steady kindly blue eyes, broad intellectual forehead, the shadow of a smile about the mouth, in part concealed by a short moustache, he sat behind a desk covered with specimens on zinc trays, and animal parasites in jars. To the nervous student a few words, bearing upon his family perhaps, for Dr. Smith had an extraordinarily wide acquaintance, and an even more extraordinary and detailed memory thereof. When human relations had sufficiently softened the official ones, the student was given an organ, for instance, asked to describe his findings and the effects of such upon its bearer during life. Whatever the student's showing, Dr. Smith ended the examination by a symptomatic reconstruction, chronologically and logically sequential, much as the paleontologist reconstructs from a lower jaw the configuration, size, age and habits of an extinct animal.

Even as Welch, of Hopkins, Smith, of the University of Texas and of the University of Pennsylvania, was one to whom students instinctively turned—for answer to medical queries, solutions of their personal difficulties, advice as to their future or present activities. To him before all others came graduates visiting their Alma Mater, assured of a cordial greeting, a vivid interest in their careers, a clear memory of their undergraduate lives and sympathetic understanding of their problems. None left him without freshened faith in themselves, renewed belief in human kindness and increased respect and affection for one so learned, so wise, so trustworthy and so elated by their triumphs, so helpful in their trials.

Having definitely crystallized his views upon a given subject, they were not readily subject to the lysis of conflicting opinion, even though this were vigorously expressed by the majority of his

faculty colleagues; nor, when overruled did he entertain other feeling than pity for the ninety and nine who were out of step. The struggle over, he was not more cheerful in victory than he was in defeat.

Associated with the encyclopedic brain was an artistic temperament, evidenced by unusual skill as a draftsman and a colorist.

In his college days Allen Smith, in addition to leading his class, from both the popular and scholastic standpoint, devoted his late night and early morning hours to the study of music, majoring in horns. He might have become a tuba virtuoso but for a protesting citizenship, a revolting student body and an unsympathetic faculty.

Into the archeology of Central America he made an excursion to which he frequently referred and with the vividness characteristic of open eyes, wide knowledge and an unusual gift for clear expression.

In the realm of sport he was an occasional duck hunter, taking pleasure therein rather for the companionship of congenial fellow huntsmen than for the kill.

Dr. Smith was an individual worker with a genius for persistence and detail. Among his many publications his *Synopsis of Studies in Metazoan Parasitology*, beautifully illustrated by himself, should take high rank. Therein are pictured and set forth many parasites heretofore undescribed.

Because of his wide knowledge, large experience and unending patience, he was sought, not only for the identification of parasites, but for the microscopic study of neoplasms, his final judgment on which was accepted without question.

He came into the world a giver, asking no return. In the service of others his strength of body, his clarity of mind, his wealth of knowledge and his material resources were equally available for the asking. He conferred a favor with the air of one who gratefully and gracefully receives it.

His last words were true to type. Past midnight, in the terminal stage of a cardiorenal death, gasping for breath, when Mrs. Smith was calling a doctor, he said, "No, I must fight this out myself."

And shortly thereafter came his lasting rest.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JUNE, 1927

ORIGINAL ARTICLES.

THE VALUE OF THE ROENTGEN RAY AS A DIAGNOSTIC AID
IN THE DIAGNOSIS OF PULMONARY AND PLEURAL
DISEASES.*

By CHARLES R. AUSTRIAN, M.D.,
BALTIMORE.

(From the Phipps-Dows Tuberculosis Dispensary, The Johns Hopkins Hospital).

A PROSPECTOR seeking to discover a deposit of precious metal may be an uninformed adventurer, who sets out upon his quest and finds his reward by mere chance. The explorer more likely to come upon Nature's treasure is one who learns what he can of the geological formation of the territory, equips himself with the tools suited for the sounding of the strata to be probed, and with the material needed to assay the worth of that which he may find.

Exploration of the chest to bring to light pathologic changes that have developed within it is not unlike the searching of the soil for gold; the relatively untutored may detect massive lesions, but the diagnostic investigator who aims accurately to locate and to define foci less gross acquires skill in all the methods he can command.

Since Laennec and his followers described methods of physical examination, members of our profession have striven to perfect them. Inspection, palpation, percussion and auscultation have been practised by all students of physical diagnosis and with the aid of these fundamental procedures most pathologic conditions of the bronchi, pleura and lungs have been recognized. Properly practised, inspection means not looking but seeing. Palpation connotes not only feeling but appreciating what is felt. Percussion signifies not merely tapping and eliciting sounds but evaluating

* Read before the Norfolk County Medical Society, December 20, 1926.
VOL. 173, NO. 6.—JUNE, 1927

what is heard, and auscultation implies that the auditor has learned to appreciate the sounds that set his tympanum in vibration. To acquire skill in the utilization of these usual methods demands not merely facility in the technique of these several maneuvers but the ability to correlate physical findings with anatomical conditions. Clinical diagnosis cannot be accurate unless he who would establish it has a knowledge of normal and pathologic anatomy and physiology.

Through the years since the foundations of physical diagnosis were laid, a superstructure of established diagnostic data has been builded by investigators equipped properly, but even when genius was coupled with technical skill in the art, many foci of bronchial or of pulmonary disease escaped detection until a necropsy disclosed them. Until Roentgen bridled the Roentgen ray and blazed the trail for other pioneers to discover how it could be employed to disclose pathologic conditions, further advance in thoracic diagnosis seemed unlikely or slow to be achieved. Within a few years, the ray came into general use as a means of thoracic exploration and some developed an attitude of skepticism as to the worth of the older methods. Many came to regard the new procedure as infallible, considered it a ready way of establishing the presence, location, extent, clinical significance, even the etiology of foci of disease within the respiratory organs. Physicians, undrilled in the school of clinical experience and unversed in pathology, made diagnoses by a shorthand method that seemed quite easy. To the experienced clinical thinker, to the student of disease, it became apparent soon that errors abounded when reliance was placed upon such isolated data, and the pathologist had a chance to jeer at his clinical brethren even more often than was usual.

From the chaos that followed the early overenthusiastic reliance upon roentgenographic data, there has evolved a more accurate estimate of the method. Experience has taught that it is an accessory; another and a valuable aid in the study of disease. Added to the facts acquired from a history, from a careful physical survey and from the clinical laboratory, the information furnished by the Roentgen ray acquires its true significance. If the comparative utility of the Roentgen ray and of other methods of physical diagnosis is to be learned, it is necessary that we have not merely technical skill and knowledge of pathologic conditions but intellectual honesty as well. For example, if one would know the value of percussion to himself, he must interpret the findings he obtains on percussion, uninfluenced by his auscultatory observation. Too often, the data elicited by one method are made to dove-tail with those that seem theoretically better to accord with facts elicited by another. Such unwarranted correlation leads to diagnostic inaccuracies, but more disastrously it leads to confusion and to failure to establish the limitations for him of a given procedure. Unin-

fluenced recording of the findings determinable by each method of diagnosis will give a true appreciation of the accuracy of each. Similarly, with the Roentgen ray. In my judgment, no one can qualify properly as a clinical roentgenologist until he has acquired a knowledge of normal structure and of pathology, and by experience learned to know how nearly he can correlate clinical and anatomic findings with the radiographic variations he notes.

In the clinic of the Johns Hopkins Hospital for the past twelve years Dr. Baetjer and I have met almost weekly and endeavored to correlate clinical and radiographic findings. Each of us had examined individuals independently of the other, recorded his findings and conclusions and then compared the data in conference. Briefly told, some of the impressions we gained are the following:

As everyone knows, to recognize the changes caused by disease it is essential that the normal be known and that the variations of the normal be established. The views we had acquired in years of desultory observation were crystalized in our concentrated study of the problem as members of the Research Committee of the National Association for the Study and Prevention of Tuberculosis. Five hundred healthy children were studied by the three groups included in that committee of six. Individuals were chosen from various strata of society, rural and urban dwellers, foreign and native born, school attendants and residents of institutions, those intimately exposed to tuberculosis and those not so jeopardized, all symptomless and apparently healthy. We were soon impressed with the fact that roentgenographically the findings varied so widely that an exact description of the normal could not be made. It became clear that the conglomerate shadow commonly designated the hilum may be regarded as normal when its lateral margins lie within the first or inner zone of the chest except when it is a solid homogeneous shadow. Calcified nodes at the root of the lungs in the absence of pulmonary abnormalities are of no significance except as evidence of some healed focus not necessarily tuberculous. Radiations of the bronchial shadows when visible in the outer or peripheral zone of the lungs were found to be evidences of inflammatory processes past or present, and when seen in the extreme apex were considered evidence of changes tuberculous in origin. Basal shadows are seen with great frequency, especially in children who have had measles, pertussis or tonsillar infections. They usually escape detection by other methods of examination. Experience indicates that such shadows may be evidence of healed processes for they may remain unchanged and unassociated with clinical symptoms over periods as long as ten years.

Similarly, the studies of this Committee have shown that the theoretically clear chest of normal adults is not readily found. The adult has weathered the storms of many respiratory infections, his respiratory tract has been assailed by dusts and irritating fumes

and the scars of the conflicts remain. Consequently, it is well to remember that many changes that would be distinctly abnormal if seen in the Roentgen ray films of the youthful chest are to be regarded as normal variations when they are encountered in the study of adults. For example, it is the rule in healthy adults roentgenographically to find moderately enlarged root shadows. These are of no significance when they do not extend beyond the middle zone of the lungs. Similarly, slight widening of the mediastinal shadow, so long as the margins are not sharply defined, does not indicate present disease any more than do calcified nodes in the root zones. Finally, the pulmonary fields of most adults show radiating, well-defined, sharp interlacing lines indicating fibrosis, and except when this change is marked it is of no moment.

The foregoing observations emphasize the need of familiarity with the changes seen in the thoracic roentgenographs of apparently healthy individuals if faulty conclusions are to be avoided.

In the study of diseases of the lower respiratory tract the Roentgen ray is useful from several standpoints:

1. It is a valuable control of the accuracy of the data furnished by other means of physical examination and thus furnishes an appraisal of the usefulness of these methods.

2. It serves accurately to locate, outline and determine the extent of foci of disease.

3. It may disclose a focus causal of symptoms in patients in whom physical examination fails to discover it because of its location or because it is masked by other conditions.

4. It gives a graphic record so that the advance or regression of the pathologic process may be followed accurately.

As a means of appraising the accuracy of other methods of physical diagnosis, the Roentgen ray is perhaps most useful in estimating the value of percussion. Every clinician can recall instances when he has elicited as the only abnormal finding a note over the lungs that was slightly or definitely less resonant than he thought it should be if the lungs were normal and yet no evidence of altered density was shown on the roentgenograph. Did this indicate the unreliability of the method of percussion? Unfortunately, data on this question are meager, largely because of the fact that the percussor has failed usually to note whether or not he considered the change he found significant and, without further study, the discrepancy is ignored or attributed to a shortcoming of the older procedure. Until clinician and roentgenologist use a terminology understandable by each, such problems will remain unsolved. If each worker affirms in every case whether or not a deviation of the note from what he considers normal in that case is significant or not, whether he considers it due to abnormalities of the thoracic wall or of the thoracic contents, pleural or pulmonary, an explanation of such discrepancies will be forthcoming. Con-

versely, when the percussion note is considered normally resonant and the radiograph shows increased density, the greater relative accuracy of the Roentgen ray in that case will be indicated and by reviewing the physical examination the investigator will acquire greater skill. When a precise terminology is utilized and correlations are established, it will not be long before each worker will appreciate the usefulness and the limitations of percussion to him in the detection of slight changes of density. Observations carried out in such fashion that clinician and roentgenologist were able to exchange views in a language understandable to each have shown that the apparent inaccuracy or shortcoming of percussion in the detection of many infiltrative lesions may be due to the fact that the infiltration is loose and contains much air, as in many cases of tuberculosis of the lungs, that many tumors and cavities are undetected by percussion because of the amount of normal lung overlying them and that hyperinflation or emphysema may mask a diminution of resonance that would have resulted from an area of increased density covered by it. Further, we believe that very slight changes in resonance unassociated with other abnormalities may be due to altered resilience of the thoracic wall.

The same comments apply, but less strikingly, to slight alterations of the breath sounds that may be detected by auscultation.

The Roentgen ray defines, localizes and measures the extent of a focus more accurately than do the other methods of physical examination. Appreciating this fact, diagnosticians of experience infer that the lesion responsible for the physical signs elicited is likely to be larger than these findings indicate. Now and again, however, physical signs suggest a focus larger than it proves to be, especially if an area of consolidation or of excavation lies juxtaposed to or in communication with a large bronchus superficially placed.

Frequently, roentgenographic study discloses the presence of hidden processes not detected by the most careful physical explorations. For example, it is an indispensable aid in the detection of a foreign body though it must be borne in mind that some forms of the latter may be pervious to the Roentgen ray and cast no shadow. When a lesion is located in the base of the lung, or when it is far removed from the parietes and without bronchial communication or contact, when it lies beneath the scapula, within the posterior mediastinum or in the trough of the diaphragm, when it is masked by emphysema or by a pleural exudate it may not be suspected until an examination with the Roentgen ray is made. Thus, it happens often that so-called silent cavities, primary or metastatic tumors, areas of beginning pneumonia, localized pneumothorax and small pleural effusions are discovered first when a radiograph is made. The presence of any of these lesions may have been suggested by the symptoms of which the patient complained or they may be an accidental finding. When a so-called miliary

seeding of the lung occurs in tuberculosis, malignant disease or pyemia, the demonstration of these multiple minute foci can be detected with assurance by the Roentgen ray when physical examination has failed to disclose them or has led to a suspicion of their existence through the auscultation of fine râles throughout a large portion of one or both lungs, unassociated with other abnormal signs. The existence of a primary neoplasm of the lung may be suggested by symptoms or by the finding of signs of consolidation in an unusual site, but oftentimes it remains for the Roentgen ray to demonstrate the presence of the mass as a dense homogeneous shadow varying in size or shape, often basal or spreading from the periphery or hilum, but usually without evidence of infiltration of the surrounding lung.

When marked thoracic deformities result from kyphotic or scoliotic curvatures or other abnormalities of the spine, normal relations become so distorted that often the site of pulmonary disease cannot be localized without the aid of the Roentgen ray. In this group of patients, however, the Roentgen ray may lead to erroneous conclusions for the shadow of compressed lung may be interpreted as due to consolidation or the dislocated vertebral bodies may be mistaken for a tumor.

Generally speaking, the progression or retrogression of a pathologic condition is evidenced sufficiently by the evolution of its symptoms and of its signs. In certain cases of pulmonary tuberculosis, however, and more particularly in those of fibroid type, when symptoms have subsided and the signs indicate the absence of anatomic activity, the Roentgen ray may show changes that appear to be a source of potential danger. So, too, a series of roentgenographs made over a period of time may give earlier evidence of the spread or of the resolution of a pathologic process than do the symptoms or the signs.

A comparison of the films made from time to time gives a graphic and permanent record of the evolution of pulmonary and pleural disease as it occurs spontaneously or influenced by therapy. Inasmuch as such studies in pulmonary tuberculosis have given much of the knowledge of the utility of the Roentgen ray in the study of pulmonary disease, some of the facts disclosed will illustrate how valuable an aid the method is in following the course of pathologic changes in the lungs.

The appearance of the youngest tubercle is unknown, though some believe it represented by the minute, ill-defined shadows designated "budding twig," "pussy-willow," "cottony" or "snow-flake" irregularities seen along the radiations of the bronchovascular tree in the subapical and apical regions of the lungs. Probably the premise is more sound than when the film shows in the upper third of the chest what is termed a "cirrhous cloud," or "soft spotty mottling," or infiltration, the conglomerate tubercle is visualized.

Such shadows are denser at the center and fade out toward the periphery to margins that are more or less hazily defined. When coalescence of such areas occurs, light areas may be seen in the zone of confluent density, indicating that consolidation is not complete. Necrosis or caseation is indicated by the appearance of areas of paling or of clearing. Cavity gives rise to a variety of appearances, a larger or smaller zone of central clearing of any shape, but often round, is bounded by a halo or rim that may be sharply or vaguely demarcated, depending upon the degree of fibrosis or of calcification of the wall of the vomica, the presence or absence of surrounding infiltration. Fluid levels may be seen within the cavity depending upon its fullness or emptiness.

The evolution of such changes can be studied with the aid of a series of roentgenographs. Increasing marginal haziness of shadows, the new appearance from time to time of ill-defined areas of increased density, coalescence of such areas, clearing of others, the appearance of shadows caused by cavities or by pleural exudation—any or all of these mutations may be noted to persist or to accompany the development or increase of constitutional symptoms, cough, expectoration, and so forth: Conversely, decreasing haziness, better definition and clearing of clouded areas may accompany or follow symptomatic improvement. Generally speaking, it is true that increasing haziness about foci predicates clinical retrogression and as the haziness decreases symptoms often subside.

On the basis of such evidence, it is conceded that moderately dense shadows with poorly-defined margins that merge imperceptibly into the surrounding texture are indicative of anatomically active foci. The hazy marginal zone is interpreted by Amberson as an inflammatory reaction due to allergy, the response that is seen when tubercle bacilli are newly implanted in the sensitized parenchyma of the lung. As the lesion progresses this haziness increases, as it regresses it clears and the shadows become smaller, more dense, better defined. Thus the correlation between clinical and roentgenographic evidence indicates that sharply demarcated, dense shadows indicate anatomically inactive disease. As the healing advances further, radiations interpreted as due to fibrosis appear—accentuated, cottony, thickened lines along the bronchovascular trunks spreading from the root zones become more sharply outlined threads that in time become intertwined, meshlike markings. Later still, these may contract and cause dislocation of the trachea and mediastinum, diminution of the volume of the chest and other deformities. In such films, too, calcification may be visualized as very dense shadows of variable size and of rounded, angular or even linear contour within the lungs, at the root or in the pleura. Not infrequently, bands of increased density along the interlobar fissures indicate pleural changes or there may be uniform, diffuse haziness when the pleura is thickened over a wider area. Oblitera-

tion of the costophrenic angle is interpreted as evidence of pleural exudation and tenting of the diaphragm and irregularities of the outline of the pericardium are considered due to adhesions.

If the significance of the changes described is appreciated, the detection of them is useful diagnostically, but it must be borne in mind that the clinical activity of a disease is determined by the presence of symptoms, by the evidence of ill health and of intoxication, factors that cannot be measured by the Roentgen ray. The usual methods of physical examination, including the roentgenograph, may indicate the anatomical activity of foci of disease, but clinical observation with the study of symptomology is needed to determine the presence or absence of clinical activity. These facts are axiomatic, but unfortunately are not always remembered.

So much for the generic description of the changes discoverable by the Roentgen ray in a given disease, pulmonary tuberculosis. How can such alterations be differentiated roentgenographically from similar ones noted in other diseases? It is the consensus of opinion that infiltrative foci within the upper third of the chest above the third rib and dorsal spine are usually of tuberculous origin, whereas changes in the basal zones, not in continuity with those in the upper thorax, are considered generally of nontuberculous causation. Further, it is a working rule, to which there are many exceptions, that changes that become more dense toward the apices are most often the result of infection with the tubercle bacillus and conversely, that lesions that increase in magnitude toward the base are of other origin, but such data are suggestive only, they do no more than suggest the likely etiology of the changes. The clinical course, the demonstration of the tubercle bacillus, the reaction to tuberculin, and so forth are needed for precise proof of causation when radiographic appearances suggest that a process is tuberculous. The truth of this is evidenced by the following: In pneumoconiosis, the radiographic appearances may simulate closely those seen in advanced bilateral tuberculosis of the lungs or in fibroid phthisis. Bronchiectatic cavities or a pulmonary abscess in an upper lobe may be confounded with vomica of tuberculous origin and miliary carcinosis cannot be finally differentiated from miliary tuberculosis of the lungs by the Roentgen ray alone. When ordinary pneumonic consolidation involves an upper lobe it may suggest a tuberculous process and only the course of the disease and the evolution of the shadow will indicate its real nature. Such confusion is less common in childhood for then the consolidation in pneumonia appears often as a triangular shadow of density, with its base at the periphery of the lung. The pulmonary mycoses, though they often lead to basal lesions and are bilaterally disposed more commonly than tuberculous foci, give rise to radiographic changes that cannot be distinguished surely from those due to the tubercle bacillus.

Though there are some who believe the contrary, the infrequent lesions of the lung caused by syphilis give no characteristic radiographic changes. Gummata, more common in the lower lobe and radiating from the root, may give a shadow like that of a true neoplasm, and gummatous infiltration may cause changes indistinguishable from those caused by the ordinary bronchopneumonia in the depth or near the periphery of the lung. The so-called nontuberculous basal lesions that are seen in the course of many infectious diseases, though known to be of different etiology, give identical radiographic appearances.

Metastatic tumors of the lung secondary to carcinoma of the prostate, of the breast, of the stomach and to hypernephroma may be suspected when round, ball-like homogeneous shadows, one or more in number, are seen in radiographs of the lungs of patients with these diseases, but they cannot be distinguished apart without collateral evidence.

Bronchiectasis may be suspected when shadows indicate an enlarged, widened bronchial tree radiating especially toward the bases, but from the radiographic appearance alone, the causation of such changes cannot be determined, unless those associated with the presence of a foreign body be excepted. The radiographic evidence of effusions in the pleural sacs—dense homogeneous shadows with a curved upper level obscuring the pulmonary markings and with dislocation of the mediastinal structures to the opposite side—gives no clue as to etiology, nor can the nature of the fluid be suspected from the shadow caused. However, the film may indicate the coincident presence of disease of the lungs when it was not detected by other means of examination and thus may suggest the nature of the underlying pathologic condition.

The presence of air in the pleural space is revealed by an abnormally clear zone in which the markings of the lung are not seen and the ribs are more sharply defined than in other parts of the chest. Fluoroscopy and roentgenography alike show the displacement of the mediastinal structures to the opposite side, provided they have not been fixed *in situ* by antecedent adhesions. The collapsed lung shows as a relatively dense, sharply limited, irregular shadow in the region of the root of the lung but when adhesions have prevented complete collapse of the lung its contour may be distorted and band-like connections with the thoracic wall may be seen. If fluid is present also, a dense opaque shadow is seen at the bottom of the chest, its upper border constantly horizontal, irrespective of the position of the patient. Localized pneumothorax may be discovered with the Roentgen ray when it is otherwise undetectable. Only occasionally, when the coincident existence of pulmonary disease is shown, can the Roentgen ray suggest the cause of the pneumothorax.

Thus far, we have discussed the helpfulness of the Roentgen ray and have said little of its shortcomings. Valuable aid that it is,

the Roentgen ray is not infallible and in no case can the utilization of it take the place of a careful physical examination and a clinical survey. Thus, we have observed several patients in whom the classical signs of lobar pneumonia were demonstrated by physical examination in whom the area of solidification underwent resolution and cleared, yet at no time did the Roentgen ray show any pathologic changes in the lung. For this discrepancy, a satisfactory explanation is lacking. Instances are numerous of patients who have had a frank hemoptysis and whose subsequent course showed the bleeding was due to pulmonary tuberculosis, yet roentgenographs disclosed no focus of disease at the time of the hemorrhage. In several instances tumors of an upper lobe of a lung have been diagnosed incorrectly as tuberculosis. Again, we have studied patients with symptoms of pulmonary tuberculosis with râles at or below an apex, with tubercle bacilli demonstrable in the sputum, the Roentgen ray films of whose chest failed to show evidence of disease. Then, too, in occasional cases of acute fibrinous pleurisy roentgenographic examination was negative even when clinical examination indicated the existence of a widespread plastic exudate.

To appreciate the helpfulness of the Roentgen ray in thoracic diagnosis is not to belittle the worth of other methods of study—to indicate the shortcomings of the Roentgen ray is not to disparage its great value. Only by recognizing the strength and the weakness of each procedure can a real appraisal of its merit be obtained. When this is done, roentgenography will be appreciated as a useful accessory method in the diagnosis of thoracic respiratory disease, but as an accessory method only; much of the usefulness of which will be lost unless the data furnished by it are correlated with those obtained from the history, the physical examination and the results of laboratory study.

Conclusions. Roentgenography has assumed a rôle of increasing importance in the diagnosis of thoracic disease, but practised as it is today by many, the use of it may be more hurtful than helpful. If the real utility of the method is to be realized, those who employ it must be trained in anatomy, pathology, physiology and clinical medicine. They must be workers who are informed of what is normal roentgenographically in the various decades of life. They must know that no examination of the chest is complete without it, but that it cannot take the place of a careful physical examination. They must understand that the Roentgen ray cannot discover fever, râles and constitutional symptoms, though it may reveal the probable cause of these manifestations.

Such workers, informed of these fundamental facts as well as of the specific limitations already mentioned, will bring to the clinician data that may confirm or deny the findings elicited by other methods, disclose the presence of undetected foci of disease, localize them, reveal their extent and texture and record graphically progressive

or retrogressive changes as they develop over periods of time. However, such data, suggestive though they may be, cannot finally determine the etiology of the abnormalities disclosed, say whether or not clinical disease exists.

Only when radiographic data are interpreted with such a background of knowledge and are correlated with all other available diagnostic criteria, will their maximum usefulness be realized. In this era of enthusiasm for so-called methods of precision, the shortcomings of a graphic method, though real, may be overlooked. The engineer has not banned the use of steam in the making of electricity since he has learned to harness the driving force of the stream, the farmer has not abandoned totally his horses since the advent of the tractor. These workers have used the new methods to supplement the old, availing themselves of the usefulness of both. Clinicians may profit by the example of artisan and agriculturalist—tried methods of physical exploration, fallible and insufficient though they may be, must not be discarded when newer methods of study become available, but the good that is in each must be adopted and all available data collated and synthesized.

SICKLE CELL ANEMIA.

WITH REPORT OF A CASE WITH AUTOPSY.

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FOLLOWING Herrick's description¹ in 1910 of a negro with peculiar sickle-shaped erythrocytes in a stained blood smear, the condition has been found not infrequently. Twenty-two active cases have been reported and approximately 100 latent cases have been mentioned. Autopsy reports have been published by Sydenstricker, Mulherin and Houseal, by Huck and by Graham. A few facts concerning this type of anemia seem definite. It appears to be limited to the negro race and so far no case has been reported except in individuals of negro parentage.

The phenomenon of "sickling" is not limited to persons with symptoms, but may be demonstrated in individuals who are apparently well but who in most instances have been related to one who has what Sydenstricker calls the active phase of the disease. In

fact Cooley and Lee¹² consider "sickling" so common that they recommend some such term as "sickleemia" for the condition when unaccompanied by symptoms, with reservation of "sickle cell anemia" for patients with definite hemolytic anemia. The phenomenon is not nearly so marked in people without symptoms. It is variable in an individual in the active phase. Subjective decline is followed by more marked changes in the blood and during periods of improvement it is sometimes difficult to get a preparation showing characteristic changes in the erythrocytes. All degrees of severity are found. The same person has been observed by Emmel to pass from the active to the latent phase, although study of the observed cases as well as our own suggests that persons with the active phase have been subnormal from birth and throughout their existence were unable to perform ordinary heavy work. Periods occurred when they were distinctly worse and were confined to bed and others when they were relatively comfortable, but never were they completely well.

Huck and Taliaferro feel that the disease is transmitted according to the Mendelian law and find that the sickling is a dominant characteristic. In the case observed by us, the boy's mother showed a few sickle cells but had no other symptoms of the disease. Unfortunately, no other members of the family were available for study.

Graham suggests that a toxic exciting agent, possibly a streptococcus, is acting on a person with an underlying status determined by deeply rooted racial characteristics. It should be mentioned that sickling has been noted in the blood from the umbilical cords of infants whose mothers showed the phenomenon.

Castana does not believe that a special semilunar anemia exists as a clinical entity with a definite symptom complex and blood picture.

In the severe active cases a definite group of symptoms and signs seem to exist, the most characteristic of which are the phenomena in the blood. The unique type of poikilocytosis which gave the disease its name is pathognomonic. The red cells, which immediately after obtaining the blood are mostly of normal shape, assume bizarre forms, the most common type resembling the crescent moon. Other peculiar forms may be seen on the accompanying photographs. Long processes at times extend from the ends of the crescents. Sickle cells may be seen in a stained smear, but are best observed in a sealed sterile cover slip preparation of the fresh blood where, after a varying time, usually from two hours to several days, practically all erythrocytes assume the typical new moon shape. The rapidity and completeness with which the change in shape takes place varies with the condition of the patient and the technique of preparation. At times sickling is marked in one portion of a slide and almost absent in another. The red cells are extremely labile and change shape with the greatest rapidity. If one removes

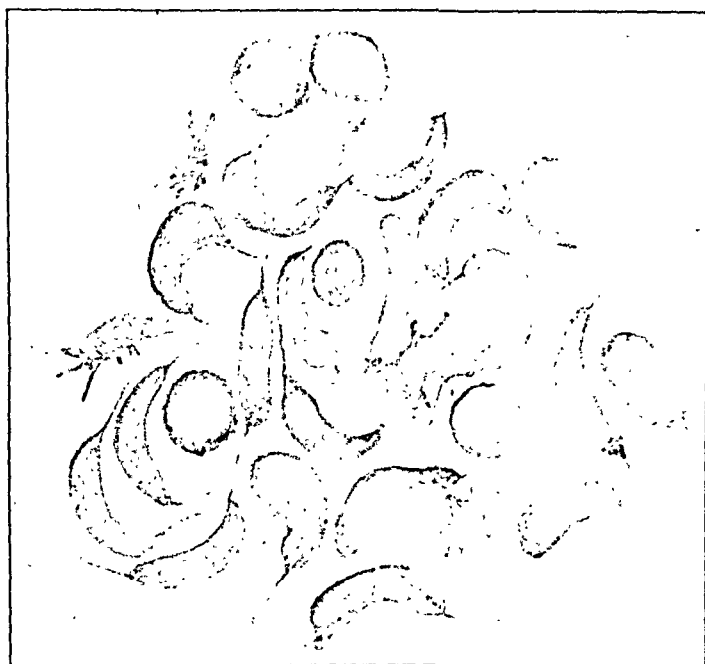


FIG. 1.—Sickle cells (unstained). Drawing from photomicrograph.

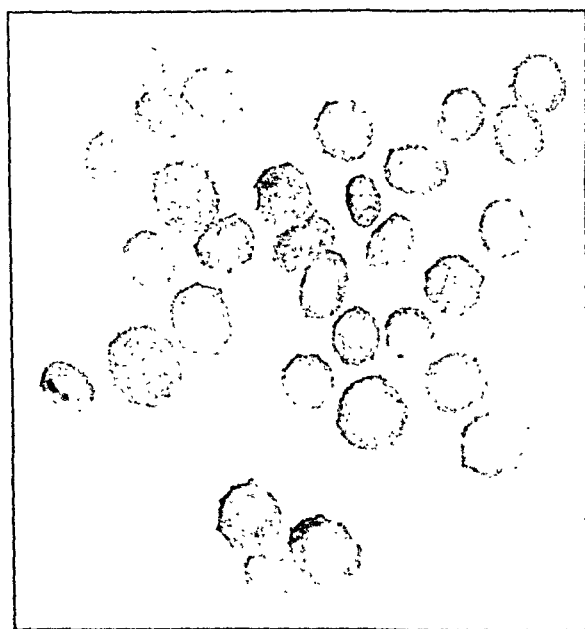


FIG. 2.—Same slide immediately after removing the coverslip. Drawing from photomicrograph.

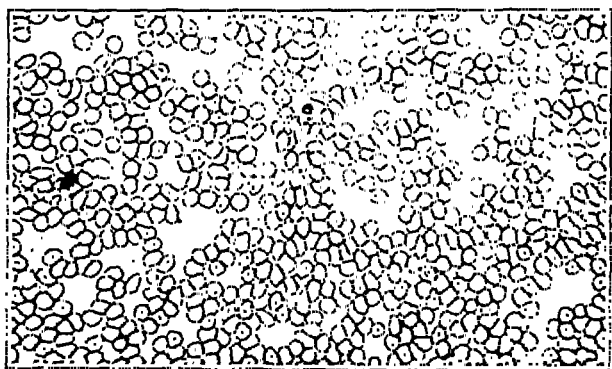


FIG. 3.—Mother's blood—photomicrograph of stained smear showing a "Sickle" shaped cell.



FIG. 4.—Patient's blood—photomicrograph of stained smear.

the cover-slip of a slide with nearly all cells of the crescent shape, it will be noted immediately thereafter that all cells have resumed a circular shape. Similarly, if the slide is left for a week or two untouched, the cells resume their original contour.

As has been noted before, the cause of the change in shape seems to lie chiefly in the cell itself and the cells of our patient developed the typical deformity in the sera: (a) of his own mother; (b) of a normal negro; (c) of a patient with pernicious anemia; (d) of a patient with the acquired type of hemolytic icterus, (e) of a patient with obstructive jaundice. Conversely, the red cells of these people did not show the phenomenon when placed in the serum of the affected negro boy. Although blood from the mother showed a few sickle cells, the son's serum did not accentuate the phenomenon. Moderate heat undoubtedly hastens the process and cold inhibits it. Bile-stained serum which had an icterus index of over 70 had no effect in either hastening the process nor in making it more complete. This varies from the results obtained by Sydenstricker, who noted a distinct acceleration. In agreement with him, we found that sodium glycocholate greatly accelerates the speed with which the change progresses while saline solution inhibits the reaction, suggesting that factors outside the cell may have some effect. Blood taken under paraffin oil and kept under oil without exposure to air shows practically no sickling whatever. Whether this is due to change in surface tension is not known.

Blood obtained by stabbing through a drop of formaldehyd placed on the skin in an attempt to get rapid fixation of the red cells shows about the same number of sickle cells as a fresh preparation observed immediately. The specific gravity of the blood in our case was low—1050 and 1048 at two different times separated by four months.

The reduction in red cells is marked, the average in the severe cases ranging between one and a half and three millions. The number of red cells decreases during acute exacerbations and rises slightly with subjective improvement but neither in our case nor in the other published cases did it approach normal at any time. The hemoglobin is proportionately reduced. Platelets are not decreased. Bleeding and clotting time are within normal limits. Anisocytosis is present and polychromatophilia is marked. The blood picture is that of marked blood destruction with very active regeneration. Nucleated red cells are common, as are reticulated cells. Sickle cells at times show a nucleus. Bilirubin is present in the plasma and the icterus index proposed by Meulengracht is markedly increased, varying between 14 and 26. The van den Bergh direct reaction is negative and the indirect positive.

In agreement with Sydenstricker and Graham, we found a downward extension of the range through which the red cells resist complete hemolysis in hypotonic salt solution.

The white blood cells vary in number. We have observed the number in the same patient varying between 7400 and 17,650. No particular increase in polymorphonuclear forms were noted. On some slides large cells, possibly endothelial in origin, formed 6 per cent of the total and, although looked for, phagocytosis of red cells by these large mononuclear cells was not noted.

Alternate relapses and remissions are the rule; the remissions may last years; the relapses as a rule are short. During the relapses epigastric pain is common and often severe. In 8 of 11 published active cases, it was present, and in our patient it was the complaint for which he sought relief. The pain is sharp and cramplike, appears at intervals sometimes of months, then occurs as often as five times a day. It has no relation to meals and may occur night or day. It sometimes is associated with nausea and vomiting. Our patient was not relieved by alkalies but the pain was entirely controlled by olive oil.

As would be expected from the marked reduction in hemoglobin, dyspnea on exertion and weakness are rather consistently present, although in 3 of 11 published cases no mention of dyspnea is made.

Jaundice is constantly present but varies in degree. At times a deepening of the yellow seems to precede other symptoms or signs in announcing the beginning of a relapse. The jaundice apparently is due to the increased blood destruction as indicated by the van den Bergh test and the finding of urobilin in the urine with an increase in the feces. Although Roentgen ray examination in our patient shows distinct shadows suggesting gall stones, there is no evidence that they are the cause of the icterus. They are common in hemolytic familial icterus and one would suspect that they would be common also in sickle cell anemia for in many ways the diseases resemble each other. Gall stones were observed in 3 of 12 cases.

A curious but striking phenomenon is the presence of ulcers in the ankle region. In 12 cases they were observed nine times. They are bilateral, multiple, sharply demarcated and heal slowly, leaving a thin shining scar. They tend to recur with relapses.

The definitely enlarged heart and loud systolic murmur with an accentuated pulmonary second sound made us uncertain whether or not the joint symptoms and fever were part of an atypical rheumatic fever. But inasmuch as such hearts are found in people with anemias, particularly of the pernicious type, and are found so consistently in people with sickle cell anemia, it is probably a part of the clinical picture of sickle cell anemia. The heart is enlarged and its rate is rapid. A systolic murmur may be heard at the apex. The liver is enlarged but the spleen is not. Over one-half of the cases reported have shown a mild generalized lymphadenopathy.

TABLE I.

[illegible]

In addition, we have a group of more uncertain symptoms and signs. Fever seems to accompany relapses. It is usually low and may have a gradual rise and decline, much resembling the type found in rheumatic fever. Most authors have noted fever but in some instances their patients had an entirely irrelevant condition which could easily account for the fever. Pain in the extremities occurs during relapses. In our case the pain was not limited to the joints but also was referred to the region between the joints. No swelling nor increase in local heat was present although swelling had been present at times and has been reported in other patients. The pain was slightly relieved by sodium salicylate but not with the promptness usually found in acute rheumatic fever. We feel that the pains in the extremities are probably part of the sickle cell anemia. Night sweats accompanied these attacks.

The Roentgen ray examination, as well as revealing shadows, interpreted as formed by gall stones, showed a consistent deformity such as is found in duodenal ulcer. With the exception of a single questionable examination for occult blood in the stools, this had no clinical confirmation. Possibly adhesions could account for the deformity, nevertheless, in the light of the unexplained occurrence of ulcers elsewhere, this region should be watched in other people showing the typical erythrocytic deformity. The presence of albumin and casts in the urine occurs often enough to require note. One does not expect to find them ten times out of twelve, particularly when the ages are between five and thirty-eight years.

The more prominent findings in the previously reported available cases have been tabulated on page 767.

Case Report. R. B. was a male negro, aged twenty years. Intermittently since his first year he had had attacks of pain in various joints, wrists, elbows, feet, ankles, knees and back, the location varying at different times. Attacks lasted six or eight months with free intervals of a year or two. Swelling of the ankles occurred at times accompanied by pain. Because of these spells he was unable to attend school or work regularly. At the age of fifteen years, following eating of green pecans, he felt severe pain in the epigastrium, vomited and was ill for two or three days. A doctor suggested that gall stones were the cause, but the father refused to permit operation.

At sixteen years epigastric pain recurred, lasting two or three weeks, and a similar attack followed at eighteen years. The last and most severe attack occurred at nineteen years. The pain occurred in paroxysms, lasting an hour or two, coming four or five times daily and leaving a distinct soreness. It radiated to each side of the abdomen—slightly more to the right. It was accompanied by persistent vomiting. He states that he had epigastric pain and joint pains, at different times, never together, although while in the hospital we observed him with both. Leg ulcers were first noted at the age of seventeen years, and accompanied the attacks of "rheumatism." He had always been jaundiced, the yellow color increasing during attacks of both types. He had infrequent headaches; was constipated, but had never had clay-colored stools. He had nocturia when ill, but not otherwise. During the spells the urine was dark colored.

The patient was born in Texas, and has lived in Texas, Arizona, Cali-

fornia, Arkansas and, as a railroad porter, "all over the country." He attended school very irregularly because of repeated illness. Besides the attacks noted above, he had whooping cough, occasional sore throat and gonorrhea. His habits were not unusual.

The patient's father died at forty-five years of age, of pneumonia. His mother is living and well at forty-four years. She shows to a very slight degree the same erythrocytic deformity as the son. The paternal grandfather died at ninety-eight years and a grandmother at eighty years. They had always been well. The maternal grandmother was killed at twenty years. The grandfather's condition is unknown. He has one brother, living and well. Two brothers and one sister died of unknown causes.

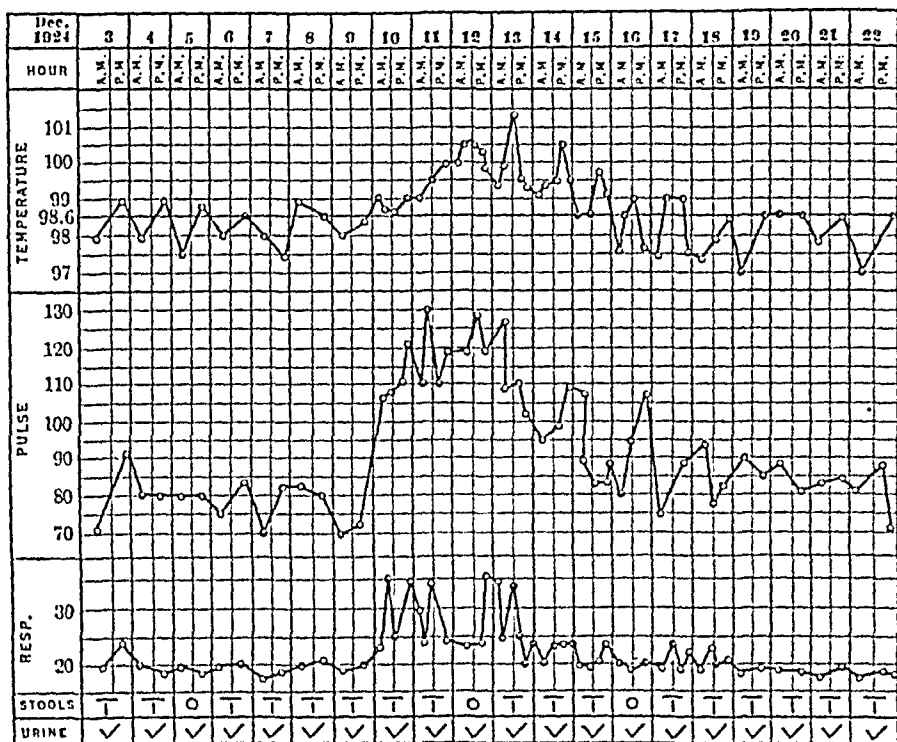


CHART.

He was normally developed and nourished. Icthyosis was present. The conjunctivæ were pale; scleræ were greenish yellow. Ocular fundi were normal. The tonsils were large. Slight enlargement of cervical, axillary, epitrochlear, and inguinal lymph nodes existed. Lungs were normal. The heart was enlarged to the left; the left border in the fifth interspace was 13 cm. to left of M. S. L. A systolic thrill was present over the whole precordia. A loud systolic murmur was heard at the apex, transmitted toward the base and the axilla. The second sound in the pulmonic area was accentuated. Blood pressure was 108/70. Peripheral vessels were negative. The abdomen, except for tenderness in the right hypochondrium and epigastrium, and a possibly enlarged liver, was normal. The edge of the liver was not felt. Spleen was not palpable. Finger nails were curved in two planes. Circular punched-out ulcers below malleoli on both legs measured about 2 cm. in diameter. A scar of a healed ulcer was present under one malleolus. Reflexes were normal. Vibratory sense was normal. Temperature, pulse and respirations are shown on the chart.

The following blood counts were taken at selected intervals:

TABLE II.—BLOOD COUNTS IN SICKLE CELL ANEMIA.

	Oct. 13.	Oct. 29.	Nov. 5.	Nov. 24.	Dec. 16.	Jan. 13.
Hemoglobin, %	40	40	50	50	58	55
Red blood cells	2,712,000	1,688,000	2,584,000	1,800,000	2,780,000	2,504,000
White blood cells	10,900	9,000	9,300	7,800	10,400	17,650
Neutrophils .	42	57	52	60	61	58
Eosinophils .	3	2	2	2	3	1
Basophils .	0	0	0	0	0	0
Large lymph.	5	7	7	5	16	2
Small lymph.	43	27	31	31	16	36
Monocytes .	3	6	5	0		
Transitionals .	4	2	2	2	2	3

Four to 11 nucleated red cells were seen to every 100 white blood cells counted. Reticulated cells varied between 6 and 12.5 per cent. Hemolysis in salt solution began at 0.34 and was complete at 0.28 per cent. Blood was Type III (Moss); specific gravity, 1050. Van den Bergh direct, negative; indirect showed a positive reaction. Icterus index varied from 14 to 26. Blood cultures were negative.

When first examined (at a time when he had fever, jaundice and epigastric pain) 90 per cent of the erythrocytes became sickle-shaped in twenty-four hours. Two weeks later, when he had no symptoms, only 10 per cent sickled after five days. During a relapse in March, 1925, when he had jaundice, joint and abdominal pain, 95 per cent of the red cells became characteristically deformed in twenty-four hours.

The cells were put in sera of persons with the following conditions:

1. Pernicious anemia.
2. Hemolytic jaundice, acquired type.
3. Obstructive jaundice (Carcinoma of pancreas).
4. Latent type of sickle cell anemia (his mother).
5. A normal white person.
6. A normal negro.

Sickling occurred in the same percentage as in the control. The cells of these people showed no sickling in the negro boy's serum with the exception of his mother, who showed a similar sickling as the control in her own serum. Cells received in oil showed practically no change in shape; and those received in normal saline showed only 5 per cent in a week. A control showed 95 per cent in twenty-four hours. Sodium glycocholate showed a marked effect in speeding up the appearance of "sickle"-shaped forms.

TABLE III.—EFFECT OF SODIUM GLYCOCHOLATE ON SICKLING.

	With sodium glycocholate.	Control.
Specimen No. 1 . . .	50 per cent in 40 min.	80 per cent in 48 hours
	90 per cent in 12 hours	
Specimen No. 2 . . .	90 per cent in 3 hours	15 per cent in 3 hours
	95 per cent in 24 "	95 per cent in 24 "

The Wassermann test was negative. The feces showed a questionable test for occult blood once only. Urobilin was increased. The urine showed the faintest possible trace of albumin, an occasional granular cast and urobilin in considerable amount.

Basal metabolism + 3 per cent.

Biopsy of an ulcer showed chronic inflammation with fibrosis and round-cell infiltration.

Roentgen ray revealed a mitral-shaped enlarged heart, a shadow suggesting gall stones and a deformed duodenum. A small six-hour residue was found. Roentgen ray of the ankles was negative.

The patient left the hospital January 26, 1925, was fairly well, and did light work as a porter in barber shops and such places for eight months. He had occasional attacks of epigastric pain relieved by olive oil, and some severer attacks which necessitated his stopping work for a few days. In November, 1925, he had a relapse marked by jaundice, joint pains, epigastric pain, nausea and vomiting. He remained at home in bed for two weeks. He was advised to reënter the hospital but began to improve, so did not. He was very well until 5 P.M. on January 11, 1926, when he had a perforation of the duodenal ulcer. He was operated upon six hours after perforation. The following day he became delirious, his pulse rose to 150 and he died on January 13, 1926.

Blood from his finger one hour after death showed many sickled forms within forty minutes, and practically 100 per cent in twenty-four hours. It took three days for these cells to return to their circular shape.

Blood from the right and left heart contained about 50 per cent sickle forms. The bone marrow had about 10 per cent crescent forms, and smears from the splenic pulp revealed slight sickling.

Through the kindness of Dr. E. M. Hall of the Department of Pathology of Stanford University, we are able to add the necropsy findings:

Autopsy.—Subcutaneous fat was normal. An ulcer was present over the right external malleolus. It measured 2 x 4 cm. and had smooth edges, while the floor was covered by granulation tissue. He had an acute purulent peritonitis. The duodenal ulcer had been removed.

The liver extended 5 cm. below the costal margin in the mid-clavicular line. It showed extreme congestion with dilatation of the capillaries and atrophy of the liver cells all through the lobules. Moderate brown pigment existed in the cells about the centers of the lobules. Round-cell infiltration of periportal connective tissue existed. The gall bladder was thickened and contained three small stones.

The spleen was shriveled and small. What appeared to be several small hemorrhagic infarcts 1 cm. in diameter were found on section. Fibrosis of the capsule and trabeculae with hyaline degeneration, necrosis and calcification were found along with marked atrophy of the pulp. The hemorrhagic areas resembled infarcts. A marked periarteritis was present. Gold-brown hematogenous pigment was found in small amounts in the fibrosed Malpighian corpuscles.

The heart was approximately twice normal size, the enlargement

chiefly in the left ventricle. The muscle showed no scarring. The right ventricular muscle showed a few small scars and some fatty degeneration. The edges of the mitral valves were slightly thickened.

The peribronchial lymph nodes were enlarged, showing a diffuse fibrosis and hyaline degeneration. Small areas of necrosis and beginning calcification were noted.

The bone marrow was deep red and the red cells varied markedly in size and shape. Numerous normoblasts were seen.

The kidneys were large. All of the glomeruli were swollen and engorged and many of the cells in the loops were sickle-shaped. The tubular epithelium was swollen, granular and showed beginning necrosis. The larger arteries showed a slight arteriosclerosis.

Conclusions. 1. The outstanding clinical features of sickle cell anemia are its occurrence in the negro, its apparent heredity, the blood phenomena, dyspnea, abdominal pain, jaundice, fever, joint and muscle pains, cardiac enlargement, absence of splenic tumor, general lymphadenopathy and leg ulcers. The blood Wassermann is consistently negative. Urine often contains albumin. Gall stones are found in some cases.

2. In this study former cases were collected and another case in the active phase added. Death resulted from duodenal ulcer and the autopsy findings are given.

3. Extreme splenic atrophy and general signs of increased hemolysis were prominent postmortem features.

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CANCER OF THE STOMACH.*

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CANCER of the stomach may, in its various forms, be one of the most hopeless or one of the most curable types of cancer. These facts, together with the difficulties in early diagnosis, the differences of opinion as to the management of the disease, and the uncertainty as to the exact relation of chronic gastric ulcer to cancer, provide questions worthy of frequent consideration. We have recently reviewed a series of 1000 consecutive cases of cancer of the stomach in which operation was performed at the Clinic, the review serving as a basis for certain facts and observations presented here.

Since 1910 more than 6000 patients with cancer of the stomach have been seen at the Clinic. The average age of the patients in the series of 1000 cases studied was fifty-four years; 37.6 per cent were between the ages of forty and fifty-five years. The number of patients seen in early life is larger than in preceding series. Recently a girl, aged twenty years, was seen, who had an inoperable carcinoma of the stomach. The oldest patient in the series was eighty-one years. The ratio between the sexes shows that the frequency of the disease in men as compared to that in women is higher than is shown in statistical studies of cancer of other parts of the body, there being 79 per cent men and 21 per cent women.

Diagnosis. The outstanding progress in the diagnosis of cancer of the stomach during the last few years can be attributed to the Roentgen ray. In spite of the generally accepted fact that the basis of successful treatment is early diagnosis, very little progress has been made in the early recognition of cancer of the stomach by the interpretation of clinical symptoms alone. Moreover, but little progress can be made because the lesion is not so situated as to cause significant symptoms until the disease is too far advanced for eradication. As a matter of fact, cancer of the stomach rarely gives rise to pronounced symptoms early; even if the lesion invades the pylorus obstruction seldom intervenes until the growth has infiltrated perigastric tissues and organs extensively.

A time-honored but unreliable sign of cancer of the stomach is that of gastric acidity. Numerous observers have shown that free hydrochloric acid can be demonstrated in the gastric contents of many patients with cancer of the stomach. In our series of 1000

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cases free hydrochloric acid was found in 43.8 per cent. In view of the fact, therefore, that early diagnosis of cancer of the stomach by clinical means is too frequently impossible because of the lack of reliable clinical signs and symptoms, progress toward increasing the percentage of cases diagnosed early enough to give the patient a chance for cure by removal of the lesion must come through a more general recognition of the fact that the Roentgen ray is the most certain method of determining whether cancer of the stomach is present. Prolonged study and observation of existing symptoms and waiting for definite diagnostic signs to develop may be justifiable in the presence of known benign lesions, but when there is a possibility of a malignant lesion in which the only chance for cure lies in early removal, such methods are dangerous. As the Roentgen ray will demonstrate 96 to 98 per cent of gastric lesions, three out of four of which are malignant, the failure to take full advantage of such an accurate method of diagnosis becomes inexcusable.

A further important fact is that in many cases in which the symptoms of gastric disease are lacking, a positive diagnosis can be made from palpable metastatic nodules, particularly on the rectal shelf, in the supraclavicular space and in the umbilicus. A biopsy of an enlarged lymph node in the supraclavicular space or umbilicus will usually identify a doubtful case not only from the standpoint of the character of the lesion in the stomach, but from the standpoint of its curability.

Indications for Operation. As a basis for the treatment of cancer of the stomach it should always be kept in mind that death will surely occur within a period of months if the disease is not interrupted in its course. The purposes in treatment, therefore, are twofold: (1) To effect cure if possible; (2) to assure the patient a minimum of suffering during the remaining months of life. In an endeavor to attain these purposes a higher percentage of patients are operated on than the picture of the disease appears to warrant, partly owing to the fact that the conscientious surgeon will practise the "golden rule" as far as the treatment of cancer is concerned, and partly to the fact that cure can sometimes be brought about in cases which, on examination, appear to be too advanced for cure. It is also true that certain patients even when the disease is obviously incurable can be greatly relieved by an operation designed only to relieve symptoms. In the light of such experiences surgeons will gradually evolve certain principles in the treatment of cancer, and will believe that exploration is warranted in any case of cancer of the stomach which is not clearly incurable because of metastasis or involvement of the cardia. On such a basis exploration is advised in more than half of the cases of cancer of the stomach observed in the clinic, and when exploration is carried out it is found that the growth can be removed in about 45 per cent of the cases.

There are certain signs and symptoms which suggest that the

disease is far advanced or that the risk of operation is unusually high. Obesity, marked anemia, rapid loss of weight in the absence of obstruction, and youth are unfavorable. The significance of this should always be pointed out to the patient's relatives. A large tumor is not necessarily an indication of inoperability. High-grade obstruction demands relief, in some cases, as imperatively as does obstruction of the colon by cancer. This results occasionally in operating on a patient who has extensive metastasis, and it is in part an explanation of the high mortality following gastroenterostomy for cancer of the stomach. The guiding principle in advising operation for cancer of the stomach is the belief that exploration is warranted in all cases in which there is no proof of the existence of metastasis.

Preparation of Patients for Operation. Much in the way of pre-operative treatment can be done to minimize the risk of operation for cancer of the stomach. Many patients who are not suffering from obstruction, but who have been on a starvation diet, are greatly benefited by a few days' rest in bed with a more liberal diet and particularly by the administration of fluids. All patients with obstruction should be admitted to the hospital. McVicar and his associates have demonstrated the importance of the recognition of the toxic manifestations of obstruction and their control by the intravenous administration of an adequate quantity of 1 per cent solution of sodium chlorid and 10 per cent solution of glucose. This is not only of great importance in the control of the toxemia, but the effect of such treatment, together with systematic lavage of a stomach which is markedly obstructed, is extraordinary. Without it the surgeon must often deal with edematous, congested and friable gastric tissue, most unfavorable for safe suturing. With the control of such mechanical obstruction and its effects the walls of the stomach, particularly the gastric mucosa, are at least partly restored to normal and the operation is rendered easier and safer.

The treatment of anemia associated with cancer of the stomach is not satisfactory. It is the custom in the clinic to endeavor by transfusion to raise the hemoglobin when it is below 40 per cent, but in the individual case such practice is not persisted in because experience has shown that unless there has been a recent massive hemorrhage, the hemoglobin can be only slightly elevated. It is probably true, however, that, even if transfusions do not increase the hemoglobin, they are of value. Moreover, if there has been recent perforation and considerable pain is present, the beneficial effects of the relief from pain following a few days' rest in bed are marked. It is, of course, unwise to sustain beyond a reasonable time such efforts to improve the condition of the patient for operation.

Operation. The first factor of safety in an operation for cancer of the stomach is anesthesia. It is well known that operations in the upper abdomen carry greater liability to pulmonary complications

than operations in other regions. This is especially true in cases of cancer of the stomach, not only because the disease and the starvation frequently incident to it have lowered the patient's resistance but because extensive resections tend to fix the diaphragm and restrict respiratory movements following operation. It is of first importance, therefore, that the danger of pulmonary complications be limited to that actually associated with the operation itself and not increased by an improperly selected or administered anesthetic.

It is safe to say that the less the general anesthesia in cases of cancer of the stomach, the less the likelihood of postoperative pulmonary complications. At the same time efforts to avoid general anesthesia in extensive operations on the stomach by carrying out the operation under local anesthesia are ill advised for two reasons: (1) Local anesthesia does not eliminate the danger of pulmonary complications; (2) greater harm is done in carrying out a difficult resection under local anesthesia in an apprehensive patient in bad condition than in performing it under a properly administered general anesthetic. Between these two extremes, that is, routine local anesthesia and routine general anesthesia, there lies a course which has been evolved through the combination of local and certain types of general anesthesia. In my own experience the incidence of pulmonary complications has been definitely decreased by the routine combination of a block of the abdominal wall with anesthesia under ethylene, oxygen and carbon dioxid, as developed by Lundy. Nothing could be more satisfactory than this combination. The field block of the abdominal wall is sufficient for the actual laparotomy and the exploration on which a decision regarding the subsequent procedure is based. If neither resection nor gastroenterostomy is advisable or possible, the incision can be closed without any further anesthesia. Should gastroenterostomy be necessary, it can practically always be performed without any general anesthesia. If resection is advisable, in many patients the stomach can be largely mobilized without any general anesthesia; the ease, the rapidity and the safety with which unconsciousness can be brought about by ethylene permits absolute control of the anesthesia with a minimum of risk to the patient. With the abdominal wall blocked in this way the general anesthetic is discontinued before the incision is closed, so that the patient is usually conscious before leaving the operating room.

It is not always easy to decide on the proper surgical procedure. In the first place the "golden rule" should again be followed, with due consideration, in cases of advanced disease, to those requests which occasionally come from patients, who because of age, important business or professional plans, or for other weighty reasons prefer to be certain of a few months of life than to undergo a great risk for a doubtful cure. Unless the cancer has been found to have penetrated into extragastric tissues to such an extent as to render

cure obviously impossible or to have involved distant organs or caused peritoneal implants, a quick decision should never be made for or against eradication. If it is obvious that the lesion is too widespread for removal, the distressing situation arising from an erroneous diagnosis should always be guarded against by the removal of tissue for microscopic examination. If the disease is confined to the stomach and the adjacent lymph nodes, a very careful examination should be made first of the upper limits of the lesion. Resection should usually be undertaken if sufficient healthy stomach is found above the limits of the growth and the stomach and duodenum can be mobilized, even if it is necessary to dissect them free from the pancreas, and even if the lymph nodes are extensively involved and apparently cannot be entirely removed. Nothing is more important in this connection than the fact that many of these enlarged lymph nodes may be found free from malignancy, and one should not be hasty in deciding against resection because of the extent of the enlargement of the lymph nodes. I recently encountered an interesting illustration of this fact in the case of total gastrectomy for a cancer of the linitis plastica type in which I was quite certain that very large unremoved lymph nodes near the esophagojejunal anastomosis were malignant. The patient succumbed to a late pulmonary complication more than a month after the operation; at necropsy the changes in these nodes were found to be inflammatory and there was no evidence of cancer.

If a tumor in the stomach can be mobilized and removed, but irremovable metastatic lesions indicate incurability, it is often in the patient's best interest to resect even though the resection is only palliative. For instance, we have had a number of patients who have enjoyed excellent health for many months, in one instance for three years, following resection of the stomach when nodules existed in the liver or implants on the pelvic peritoneum. Furthermore, there are at times very clear indications for removing small obstructing growths at the pyloric end of the stomach, although metastasis has made the disease incurable. Resection under such circumstances is followed by better and more lasting results than gastroenterostomy.

Gastroenterostomy is useful in two types of cases. The first type is that in which the operation is performed solely as a palliative measure, the palliation being real when the cases have been well selected. It should be remembered, however, that in cases of advanced disease the musculature of the uninvolved portion of the stomach is so impaired by obstruction and poor nutrition that the anastomosis may not function well. The operative mortality of gastroenterostomy for cancer is higher than that of resection. In the second type gastroenterostomy is performed as a preliminary stage to resection. Crile has emphasized the importance of this, and there are occasional cases in which resection as a secondary

procedure can be safely accomplished where it would have been doubtful as a primary procedure. Since we have been giving more attention to the preparation of patients before operation we find the necessity of the two-stage operation occurs less often. When it is desirable to relieve obstruction, fixation of the stomach posteriorly may not permit of satisfactory posterior gastroenterostomy, in which event an anterior gastroenterostomy should always be substituted for the attempt to force a posterior.

When resection is indicated there are many methods of restoring gastrointestinal continuity. Basically there are two: Either a direct union between the stomach and the duodenum or the closure of the duodenum and a union of the remaining portion of the stomach with the jejunum. The former method, the Billroth I, is useful, time saving and safe if all precautions are taken against accidents. In cancer, except in the very small lesions at the pylorus, it is questionable whether the Billroth I constitutes as thorough an operation as the Billroth II or its modifications. A further disadvantage in the Billroth I is that if recurrence takes place it is likely to do so in the neighborhood of the new anastomosis and cause obstruction.

The chief points of importance in carrying out the Billroth I are: (1) Many interrupted sutures should be used in completing the anastomosis; (2) the anastomosis should be held to the right of the median line by a suture between the pyloric end of the stomach and the round ligament of the liver to prevent strain on suture lines; (3) the retention of gastric contents should be carefully avoided by routine lavage during the few days following operation; (4) no food should be permitted for four or five days following operation.

Of the different methods of restoring continuity by union of the stomach and the jejunum the anastomosis between the end of the stomach and the side of the jejunum has attained the greatest popularity, largely because it consumes less time than the Billroth II. The gastrojejunal anastomosis can be made either behind the colon or in front of it. The posterior method can be used in many cases without difficulty; but when after extensive resection, only a small segment of stomach is left, it is simpler and safer, and less likely to give rise to complications to bring a long loop of jejunum up in front of the colon and attach it to the end of the stomach. When this operation is completed the two loops of jejunum should be united opposite the duodenojejunal angle by a small anastomosis which prevents retrograde distention of the duodenum and obviates the possibility of danger from that source.

The care of the patient following operation is a very important factor in safety. All patients are given an adequate amount of morphin and atropin, and nothing is permitted by mouth for three, four or even five days. Fluids are maintained by hypodermoclysis and, if necessary, intravenous administration. The

stomach tube should be used without the slightest hesitation. We are becoming more and more convinced that in every case after partial gastrectomy a tube should be passed and the stomach irrigated within twelve to twenty-four hours after operation and subsequently as necessary. The cleansing of the stomach of old blood clots and gastric secretions is at least appreciated by the patient and aids greatly in restoring tone to gastric musculature.

Results from Operation. The results of the surgical treatment of cancer of the stomach should always be considered in the light of the outcome of the uninterrupted course of the disease which is certain death, often preceded by periods of great suffering. While operative mortality is not of primary importance in such a disease, it should be kept at the minimal point which will not deny patients the chance for cure or the relief from distressing symptoms which surgery affords. The mortality following operations for cancer of the stomach can be markedly lowered by scrupulous attention to the preoperative treatment just outlined. If the physician coöperates with the surgeon in maintaining this care after operation the risk is reduced to a minimum, as is shown by a report of a series of 113 consecutive operations for cancer of the stomach. In 46 cases the operation was partial gastrectomy, with one death, which occurred in a case of extensive carcinoma invading the pancreas.¹ Thus far this year in the Clinic partial gastrectomy has been performed in 85 cases, with death in 5.*

The end-results of partial gastrectomy for cancer of the stomach depend primarily on the extent of the disease, although unexpected cures in advanced cases indicate, as in the treatment of cancer in other situations, that other factors are connected with the question of cure and recurrence. Based on the extent of the disease alone, our series of 1000 cases showed that 52 per cent of those patients in whom the lymph nodes were not involved were alive and well at the end of three years, while 19 per cent of those whose regional nodes were involved were alive at the end of three years. These figures do not take into account the normal death rate of persons at this period of life.

In those patients who eventually succumb to the disease following partial gastrectomy the protection afforded by the operation against distressing symptoms is marked enough to lead us to remove the growth more frequently for palliation only. We have already referred to the results of gastroenterostomy as a palliative measure; although the relief of marked obstruction is sometimes imperative, it should be remembered that the operation is of considerable risk because of the patient's condition incident to an inoperable cancer, and that the average length of life following gastroenterostomy is

* Data for the year 1926 show a total of 120 cases of partial gastrectomy for cancer, with death in eight.

seven months. This is only one month more than the average duration of life in the cases in which no operation is performed.

The all-important facts in connection with cancer of the stomach at present are that early removal of the growth gives a good prospect of cure and that, of our present facilities for detecting the disease early, competent roentgenologic examination is paramount. The status of the surgical treatment of cancer of the stomach has been aptly described by Moynihan, "Surgery has been made safe for the patient; we must now make the patient safe for surgery."

Summary. A series of 1000 cases of cancer of the stomach forms the basis of a review of the general problem of this disease. Change in gastric acidity and symptoms of obstruction are inconstant in the early course. The Roentgen ray provides an almost infallible method of diagnosis and should always be used.

Unless there is clear evidence of metastasis, operation is justifiable. Exploration at least was undertaken in more than half of the series, and in almost half of these the growth was removed. Obesity, anemia, rapid loss of weight and youthfulness of the patient add to the risk of operation and diminish the prospect of cure.

The liberal administration of food and fluids combined with rest in bed, and the intravenous use of sodium chlorid and glucose before operation tend to minimize the risks and enhance the prospects of a good result.

Regional anesthesia will suffice for incision and exploration, but general anesthesia is necessary for a difficult resection, especially if the patient is apprehensive.

The types of resection are discussed and preference given to gastrojejunal anastomosis, which should be carried out in the anterior position when the gastric stump is small. The latter operation should be combined with jejunojejunostomy. No food is given for several days after operation, and fluids are administered extraorally. Lavage of the stomach is desirable, even as a routine on the first day.

The operative mortality is much improved by the preoperative care and by coöperation with the physician. To illustrate this fact reference is made to a series of 46 consecutive cases of partial gastrectomy for cancer of the stomach with death in 1, and to the entire series in 1926, in which death occurred in 8 of 120 cases of partial gastrectomy for cancer.

The end results in the series of 1000 cases are discussed: If the lymph nodes were not involved 52 per cent of the patients were alive at the end of three years; otherwise only 19 per cent of them survived that long.

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MIGRAINE—ITS TREATMENT WITH PEPTONE AND ITS FAMILIAL RELATION TO SENSITIZATION DISEASES.

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TWENTY-FIVE cases of migraine treated with peptone have previously been reported by Miller and Raulston.¹ This report is based on a study of 20 additional cases of migraine, all private patients of Dr. Joseph L. Miller and all of whom have been under our observation for periods of two to sixteen months. They comprise all of the cases of migraine treated with peptone in that period. All of the patients reporting to the office with migraine were not treated with peptone. The severe cases which had received no benefit from other medication were given peptone at once, but patients who had never consulted a physician or who exhibited the disease in a milder form were simply told of the nature of migraine and advised as to their habits and manner of living. Others were given *cannabis indica* which not infrequently afforded relief. When these measures failed, small doses of iodides (5 to 10 gr. daily) were often prescribed. Liveing² quotes Salter "that 20 per cent of asthmatic patients will be relieved by the administration of iodides." Liveing, thinking that migraine was in some way related to asthma, placed his migraine cases on this treatment with good results in several instances. We have witnessed some good effects when iodides were administered for long periods, but apparently little change occurred for several weeks after the treatment was begun. One patient with migraine and a simple goiter was given a drop of the saturated solution of sodium iodide once a week for the goiter. Some months later she reported that the medicine had reduced the goiter and that the headaches had also disappeared. Recently a nurse who had had a very severe migraine, and who had not benefited by treatment with *cannabis indica* or peptone, reported that she had not had a headache for over seven months. She had taken iodides for six weeks previous to the cessation of the headaches and had continued taking six drops twice daily ever since. She was doing the same work and there were no other factors that we could determine that could have controlled her headaches. Just what the action of the iodide is, is not known.

Patients who received no benefit from the types of therapy noted above, were then treated with peptone.

Method of Treatment. Patients are given an initial dose, intravenously, of Armour's 5 per cent peptone solution, followed every three to four days by further injections, increasing the dose 5 minims each time until maximum doses of 25 minims each are attained. Successive injections are then kept at that maximum dose. If no benefit ensues after a series of from 8 to 10 injections, the treat-

ment is discontinued and considered as a failure. If, however, a favorable result is obtained, the time interval between injections is lengthened gradually until the longest interval is found which will insure freedom from headache, and injections are continued accordingly. Marked variation in the time interval between injections was noted, many needing an injection every three to five weeks while a few needed injections at much longer intervals. Miller and Raulston reported one patient with complete relief for a period of nine months. When the headaches recur, as they do when the interval is too long, 3 or 4 peptone injections at close intervals seem to control them again. This latter feature has been so striking that we have regarded it as evidence of the rôle of desensitization in the treatment of migraine. Hay fever and asthma behave similarly when treated with pollens or other proteins. The desensitization there is also a temporary one.

Results of Treatment. The cases have been classified into three groups according to the benefit derived; markedly improved, improved, and failures. The "markedly improved" are those cases in which the patients experienced complete relief and could be kept practically free from headache by further injections. They might have had very mild headaches at intervals of six to eight weeks, but never had the severe type previously complained of; and if the headaches reappeared after the peptone had been discontinued for periods of several weeks or longer, complete relief was obtained by resuming the treatment. Those considered as "improved" could not be entirely controlled by peptone, but experienced considerable relief in that the headaches were not nearly so severe and were much less frequent. These patients willingly continued treatment because of the relief from their symptoms. "Failures" are those not distinctly benefited or those in which the relief was insufficient to justify further treatment.

Ten cases (50 per cent) of this series were classed as failures, 7 (35 per cent) as markedly improved and 3 (15 per cent) as improved. Of the failures 2 patients thought that they had been helped, but we did not feel that the improvement claimed was sufficient to justify further treatment. In the 25 cases, reported by Miller and Raulston, 9 (36 per cent) were considered much improved, 12, or 48 per cent, as improved and 4, or 16 per cent, as failures. Their results were somewhat more favorable, possibly due to the fact that they prepared their own peptone and obtained many more protein reactions than now occur with the use of Armour's peptone.

Discussion. There seems to be no method of determining in advance which patients will receive benefit and which will not receive benefit from the treatment. Age is not a factor. Sex, previous duration of the disease, family history of migraine or of other sensitization diseases do not seem to be of any assistance. Four to 6 doses of peptone, in favorable cases, usually or, one might say, almost invariably, offer encouragement in that patients will state

that they feel as though they are going to have a headache but it does not mature; often those patients who have visual disturbances or other warnings preceding the headache may even have these symptoms but the attack stops there. Other indications are the lessened intensity of the headaches and the longer intervals between attacks.

The question of dosage has been a problem. All cases were given an initial dose of 5 minims and increased 5 minims each dose. At first they were kept at a maximum dose of 15 minims, but when no improvement occurred after six to eight doses, the amount was gradually increased to 25 minims at each injection, and this amount has never been exceeded intravenously. In this series, it is my impression that better results have been obtained with the larger doses. Subcutaneous injections as large as 3 cc. have been tried both in some of the failures and some of the markedly improved. None of the failures by the intravenous administration were benefited by the subcutaneous method. This latter method had some disadvantages in that pain was often produced for several minutes at the site of injection and not infrequently the arm was sore for several hours afterward.

One patient (V. B. No. 15) had a chill followed by a temperature of 102° after two successive (third and fourth) intravenous treatments of 15 minims each. She has continually received the same or larger dosage since then without any harmful effect. Just what caused the reactions is not definitely known. The ampules had not been opened until the time of giving the medication and presumably were sterile. Two other ampules from the same lot were cultured and no growths were obtained after seven days' incubation. It is possible to get this reaction with contaminated peptone, but the more likely possibility is that these ampules contained more proteose than usual. Witte's peptone, which has a higher percentage of proteose, often causes such a reaction. This reaction is of no special consequence except that it is very uncomfortable to the patient.

Three of the failures were given courses of tuberculin without benefit. This was used because of the rather striking results which van Leeuwen³ has reported in asthma by the use of tuberculin subcutaneously.

The essential features of each case are recorded in Table I.

Migraine and its Familial Relation to other Sensitization Diseases. Living⁴ quotes Tissot⁴ as being the first to report migraine as a familial disease. Subsequent writers have never failed to recognize this factor. In 1920, Buchanan,⁵ in his studies at the Mayo Clinic, concludes that migraine is transmitted to the offspring in accordance with the Mendelian law and, therefore, is of definite hereditary nature. Timme,⁶ on the other hand, believes migraine and epilepsy are so-called "unit-characters" and that a study of their transmissibility is out of the question because of the many varied types that occur.

TABLE I.

Name.	Sex.	Age.	Duration of migraine.	Family history of					Eyes signs.	Nausea.	Vomiting.	Number of attacks per month.	Food sensitization.	Time treated.	Results.	
				Asthma.	Hay fever.	Migraine.	Epilepsy.	Hives.	Eczema.						Markedly improved.	Failed.
D. P.	♀	28	2 yrs.	-	-	Pt. +	-	-	-	+	Rarely +	0-8	-	3½ mo.	+	+
E. P.	♂	17	2 yrs.	-	-	Pt. +	-	-	-	+	-	Almost daily	-	2 mo.	+	+
H. G.	♂	24	18 yrs.	-	-	Pt. +	-	-	-	+	+ early in life	Almost daily	-	2 mo.	+	+
W. I.	♀	33	25 yrs.	-	-	+ Pt. mother, aunt ♀	-	+ brother	-	-	+	3-4	-	3 mo.	+	+
W. C.*	♂	56	10 yrs.	-	-	Pt. +	-	-	-	+	-	3-5	-	16 mo.	+	+
L. S.*	♀	40	20 yrs.	-	-	Pt. + mother ?	-	+ Pt. in childhood	-	+	+	4-6	+ Chocolate, skin test neg.	13 mo.	+	+
W. M.	♀	46	20 yrs.	-	-	Pt. + grand-mother ♀	-	+ Pt. in childhood	-	-	-	3-4	-	0 mo.	+	+
A. B.	♀	27	Many years	-	+ uncle ♂	+ Pt. mother, grand-mother, mother, aunt +	♀	-	+ grand-mother ♀	-	-	1	-	3 mo.	+	+
M. S.	♀	31	3 yrs.	-	-	mother pt. +	-	-	-	-	+	3-1	-	0 mo.	+	+
J. W.*†	♀	21	Many years	-	-	father pt. + Pt. grand-mother ♂	-	+ Pt. in childhood	-	-	-	3-6	-	4 mo.	+	+
D. G.*†	♀	63	60 yrs.	-	-	mother ♂	-	-	-	-	-	2-3	-	6 mo.	+	+
H. O.	♀	38	25 yrs.	-	-	Pt. + mother, father, 3 S. & 1 B. + Pt. mother, sister	-	-	...	+	+	3-4	-	15 mo.	+	+
D. O.*	♀	20	10 yrs.	-	-	Pt. + mother pt.	-	-	-	+	+	2-4	-	3 mo.	+	+
V. B.	♀	42	30 yrs.	-	+ Pt. father	+ Pt. mother, aunt ♀	-	-	-	+	+	2-4	-	3 mo.	+	+
W. W.*†	♀	25	7 yrs.	-	brother, uncle ♀	-	-	-	-	+	+	2-4	-	14 mo.	+	+
C. H.	♀	10	Several years	-	-	+ Pt. mother, aunt ♀	-	-	-	+	+	2-6	-	15 mo.	+	+
D. H.	♀	21	Many years	-	-	Pt. + father, uncle ♂	-	-	-	+	+	1-3	-	15 mo.	+	+
T. S.	♀	39	Many years	-	-	+ Pt. father, brother pt.	-	-	-	-	-	1-3	-	24 mo.	+	+
C. C.	♂	31	6 yrs.	-	-	-	-	-	+ Pt.	+	+	1-3	-	24 mo.	+	+

* Subcutaneous pyrene tried † Tuberculin tried ♀ = maternal. ♂ = paternal. 7 (35%) 3 (15%) 10 (50%)

Asthma, hay fever, urticaria and some forms of eczema are usually considered as anaphylactic diseases, while migraine and epilepsy appear to have many factors in common. Miller and Raulston have previously reported some evidence of the anaphylactic character of migraine, and Miller⁷ reviewed the evidence of idiopathic epilepsy as a sensitization disease. Migraine and epilepsy have long been thought to be associated conditions. Liveing speaks of the two diseases as being interchangeable and thought them to be different manifestations of the same disease. Wilson,⁸ Oppenheim,⁹ von Vorkastner¹⁰ and many others call attention to the intimate nature of migraine and epilepsy. Buchanan¹¹ believes that a person with migraine is more likely to produce epileptic offspring than the epileptic himself. In two series of epileptics, each of 128 cases, migraine appeared in the ancestral, personal history or in brother or sister in 53.9 per cent and 66.4 per cent. A history of epilepsy was present in only 10 per cent.

Gowers¹² and Möbius¹³ speak of the not infrequent development of asthma in patients suffering with migraine. Adkinson¹⁴ believes that asthma behaves as a true inherited trait. In 400 cases studied, 48 per cent gave a history of asthma occurring in other members of the family. Adkinson also concludes that when protein sensitization does run in a family, it is not identical as regards either specific proteins or clinical manifestations developed in different members of the family. Hay fever, some urticarias and, occasionally, eczemas are considered as other manifestations of protein sensitization. Eczemas associated with asthma are usually anaphylactic, according to Ramirez.¹⁵ Walker¹⁶ cites cases of asthma which had eczema, urticaria and angioneurotic edema caused by the same protein. Cooke and Vander Veer¹⁷ reviewed the family histories of 621 cases of human sensitization in which asthma, urticaria, angioneurotic edema and acute gastroenteritis were considered as manifestations. In 504 cases with satisfactory histories, there was a positive antecedent, direct or collateral history in 48.4 per cent. Rackemann¹⁸ believes that patients inherit idiosyncrasies to foreign proteins in 55 per cent of cases. Spain and Cooke,¹⁹ in studying the familial occurrence of hay fever and bronchial asthma, found that 58.4 per cent of the 462 cases studied gave a positive antecedent history. In normal families this is only 7 per cent. Van Leeuwin and Zeydner²⁰ have isolated from cases of asthma, urticaria, epilepsy and migraine, a substance which stimulates smooth muscle. This substance was not present in many other diseases tested, and it remains to be seen whether this substance will prove to be a constant factor in these disorders.

Clinically, migraine seems to be associated with asthma, hay fever, urticaria, epilepsy and eczema in the family history of a large number of cases. We were anxious to confirm this impression and to determine which of these diseases, if any, were the most closely

related. Consequently, the records of 1000 consecutive cases coming to the office for general advice and diagnosis have been studied and summarized. Each patient was carefully questioned concerning the occurrence of these diseases in any member of the family, including the grandparents. It is admitted that many errors doubtless occur in obtaining such information, chiefly because people do not remember as much about their families as we would like to have them. However, the questions were asked in many different ways, and the information obtained is reasonably accurate. The following tables summarize this data:

TABLE II.—MIGRAINE IN 1000 UNSELECTED FAMILY HISTORIES.

	Per cent.
Migraine occurred in 261 families	(26.1)
Associated with asthma	60 (22.9)
Associated with hay fever	35 (13.4)
Associated with urticaria	73 (27.9)
Associated with epilepsy	10 (2.6)
Associated with eczema	25 (9.5)
Associated with migraine	120 (45.9)
Migraine occurring alone	70 (26.8)

TABLE III.—ASTHMA IN 1000 UNSELECTED FAMILY HISTORIES.

	Per cent.
Asthma occurred in 162 families	(16.2)
Associated with migraine	60 (37.0)
Associated with hay fever	45 (27.7)
Associated with urticaria	40 (24.6)
Associated with epilepsy	5 (3.0)
Associated with eczema	17 (10.5)
Associated with asthma	30 (18.5)
Asthma occurred alone	53 (32.7)

TABLE IV.—HAY FEVER IN 1000 UNSELECTED FAMILY HISTORIES.

	Per cent.
Hay fever occurred in 91 families	(9.1)
Associated with migraine	35 (38.4)
Associated with asthma	45 (49.4)
Associated with urticaria	29 (31.8)
Associated with epilepsy	2 (2.2)
Associated with eczema	12 (13.1)
Associated with hay fever	10 (20.9)
Hay fever occurred alone	19 (20.9)

TABLE V.—URTICARIA IN 1000 UNSELECTED FAMILY HISTORIES.

	Per cent.
Urticaria occurred in 191 families	(19.1)
Associated with migraine	73 (38.2)
Associated with hay fever	29 (15.1)
Associated with asthma	40 (20.9)
Associated with epilepsy	9 (4.7)
Associated with eczema	4 (2.0)
Associated with urticaria	21 (10.9)
Urticaria occurred alone	72 (37.6)

TABLE VI.—EPILEPSY IN 1000 UNSELECTED FAMILY HISTORIES.

	Per cent.
Epilepsy occurred in 27 families	(2.7)
Associated with migraine	10 (37.0)
Associated with asthma	5 (18.5)
Associated with hay fever	2 (7.7)
Associated with urticaria	4 (14.8)
Associated with eczema	4 (14.8)
Associated with epilepsy	1 (3.7)
Epilepsy occurred alone	8 (29.6)

TABLE VII.—ECZEMA IN 1000 UNSELECTED FAMILY HISTORIES.

	Per cent.
Eczema occurred in 61 families	(6.1)
Associated with migraine	25 (40.9)
Associated with asthma	17 (27.8)
Associated with hay fever	12 (19.6)
Associated with urticaria	4 (6.5)
Associated with epilepsy	4 (6.5)
Associated with eczema	13 (21.3)
Eczema occurring alone	11 (18.0)

Comment. Migraine occurred in 261 (26.1 per cent) of the 1000 unselected family histories. It occurred once in the family history, and unassociated with any of the other diseases, in 70 (26.8 per cent) of the 261 families with migraine. It was associated with migraine in other members of the family in 120 (45.9 per cent). Other than showing this one association migraine occurred alone in the history as frequently as it was associated with any of the other diseases.

Of the 162 (16.2 per cent) families in which a history of asthma was present, it occurred alone in 53 (32.7 per cent). It was associated with migraine in 60 (37 per cent), this being the only instance where it was associated more frequently with another disease.

Hay fever occurred alone in 19 (20.9 per cent) of the 91 families in which it was present. It was associated with asthma in 45 (49.4 per cent) and migraine in 35 (38.4 per cent).

Urticaria occurred alone as frequently as with anything else. Epilepsy occurred alone in 8 (29.6 per cent) of the 27 families in which it was present. It was associated with epilepsy in 3.7 per cent and with migraine in 37 per cent. This seems to support Buchanan's report, although here there is a very limited number of cases. The study with eczema revealed nothing except the large percentage of cases associated with migraine. Eczema occurred alone in 18 per cent, was associated with itself in 21.3 per cent and with migraine in 40.9 per cent.

It is very difficult to draw conclusions from statistics of this sort, and I am hesitant in doing so. The figures do not present the striking relationship between these diseases which we had expected to find. Aside from the few instances commented on, the different diseases occur alone as frequently as they are associated with any of the other diseases.

The cases reported here are from the private practice of Dr. Joseph L. Miller. It is through his suggestion and because of his interest in the subject that this study was undertaken.

Summary. 1. Twenty consecutive cases of migraine treated with Armour's 5 per cent peptone are reported. Ten (50 per cent) were failures, 7 (35 per cent) were markedly improved, and 3 (15 per cent) were improved.

2. One thousand unselected family histories are summarized with reference to the occurrence and association in them of migraine, asthma, hay fever, urticaria, epilepsy and eczema.

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AURICULAR FIBRILLATION ASSOCIATED WITH HYPERTHYROIDISM.

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THE importance of recognizing the presence of auricular fibrillation in cases of hyperthyroidism has led us to offer this report of 120 cases in which this condition has been studied with special reference to the response to certain therapeutic measures. From the fact that J. Phillips, in 1922, in an article on "cardiac disturb-

ance associated with disease of the thyroid gland," used as an illustration 1 case of adenoma of the thyroid gland in which auricular fibrillation was present, Baumgartner, Wells and Schoonmaker have recently concluded that the association of auricular fibrillation with hyperthyroidism has been observed infrequently in the Cleveland Clinic. In view of the frequency with which this condition has been seen, and the importance of its recognition, already referred to, the conclusion on the part of these authors was unfortunate. On the contrary, this condition has been made the subject of special study, certain aspects of which are included in this presentation.

In every case in the group of cases reported here the auricular fibrillation was either secondary to, or had been aggravated by, the hyperthyroidism. In some cases, however, the auricular fibrillation had been present before the onset of the hyperthyroidism. For example, in 1 case the heart action had been irregular for twenty years, and in another heart trouble had been present for fifteen years. Some patients stated emphatically that the heart action had been totally irregular in the same way as when we first saw them for periods varying from ten to twenty years, whereas the symptoms of hyperthyroidism had been manifested only for periods varying from a few months to a few years. A few patients gave a history of the occurrence of an acute nervous spell, or of a nervous breakdown with a marked tremor and a marked loss in weight in spite of a voracious appetite, as long as fifteen years before we saw them, these symptoms being accompanied by paroxysms of irregular heart action. In 1 such case there had been complete irregularity of the heart action throughout the preceding fifteen years; in this case a very pronounced hyperthyroidism was found, which the patient had not suspected.

When no irregularity of the heart action precedes the onset of hyperthyroidism, the alteration in the action of the heart generally progresses in the following sequence: There is first a simple tachycardia or a reduplicated sound with gallop rhythm. Cardiac dilatation then develops, and when this has progressed sufficiently the ring of the mitral valve apparently becomes relaxed so as to allow a functional mitral regurgitation. If this condition persists without relief, then in many cases irregularities develop such as extrasystoles, paroxysmal tachycardia, paroxysmal fibrillation, persistent fibrillation and occasionally flutter.

Among this group of irregularities of the heart action auricular fibrillation is most frequently encountered and is the most serious, since the ventricular rate often ranges from 140 to 200 and a certain degree of heart failure is quickly developed. Cases in which the auricular fibrillation is persistent and the heart failure has progressed so far that a general anasarca is present are always desperate risks. Among the cases covered by this study auricular flutter

has been present in only 1 case, and atypical flutter has also been present in only 1.

The average age of the patients in this series is fifty-two years, only 3 being under forty years of age—twenty-four, thirty-five and thirty-nine years, respectively.

It is obvious that in view of the serious risks presented by these cases the plan of management is of vital importance. Operation is urgently indicated for the relief of the hyperthyroidism, and it is obvious that in many cases the prognosis of the condition of the heart is hopeless without radical treatment. The plan of management, therefore, must be directed to improvement of the action of the heart to a degree which will diminish the operative risk as far as possible. This plan of preoperative management includes absolute rest in bed with medication with Lugol's solution, digitalis, novasurol, ammonium chlorid and sedatives or narcotics as indicated.

In spite of the fact that in the group of cases under consideration 40 per cent showed slight heart failure, as manifested, for example, by basal râles, an enlarged liver and edema of the legs, and that in 20 per cent heart failure had progressed so far that general anasarca was present, 97 per cent improved sufficiently for ligation or lobectomy to be attempted. Of the cases not operated upon 2 died before an operation could be performed, 1 of influenzal pneumonia, the other of streptococcic sore throat; in 1 case operation was contraindicated by the presence of diabetes. In 60 per cent of the cases operated upon, ligations preceded the thyroidectomy. In the remainder thyroidectomy was performed at once.

In 32 per cent the action of the heart became regular after operation. Quinidin was used in 3 cases, 2 of which responded well, 1 of these requiring only one dose of 5 gr. In the second case 15 gr. of quinidin were given daily for four days after thorough digitalization, without any resultant effect upon the rhythm of the heart, but the patient reported that the heart action suddenly became regular one month later, after she had returned home. In the third case an average of 12 gr. was given daily for five days before the action of the heart became regular. In those cases in which fibrillation precedes the onset of hyperthyroidism it is not to be expected that either thyroidectomy, or thyroidectomy plus treatment with quinidin will make the heart action regular, but that fact should be no contraindication for an operation.

Of the 12 fatal cases in this group all were extreme risks in which the prognosis was hopeless without operation. In 1 of these cases the action of the heart became regular under treatment with digitalis, but a partial heart block developed. This cleared up, however, as was shown by an electrocardiographic tracing. Several weeks after the patient returned home she died suddenly. No autopsy was performed, but one may well question whether death may not have been due to a cerebral or cardiac embolus.

In only 2 of the cases in which the action of the heart became regular after the operation has an irregular heart action recurred. In 1 of these cases quinidin controlled the heart action for a year or more, but it has now become persistently irregular. This patient, however, is able to keep the heart rate under control and to carry on his daily business comfortably. In the other case fibrillation recurred during an attack of influenza and has become permanent. Of those cases, 44 per cent of the total series, in which the heart action did not become regular after operation, 24 per cent are very comfortable. The remaining 20 per cent have had to reduce their activities considerably, but this permanent reduction of activity cannot be said to be due entirely to the hyperthyroidism or to the condition of the heart. Thus, in 2 cases there is a marked hypertrophic arthritis, 1 of these patients having broken his hip during the period between the ligation and the thyroidectomy. Moreover, in every case in the group there is a pronounced arteriosclerosis which, quite apart from the hyperthyroidism, would have reduced the activities of the patient considerably.

Nine patients take digitalis regularly and 5 are not taking digitalis. In 2 cases in the latter group electrocardiographic tracings show a heart rate of from 70 to 80, so that it may be assumed that they have a physiologic auriculoventricular block which maintains the normal rate. Many patients dislike to take the amount of digitalis that is required to control the heart action, and will not do so unless the advisability and the reason for it are thoroughly explained to them. After such an explanation, however, they are usually very faithful.

As for the use of digitalis before the operation or between the ligations and the lobectomy, that is, before the hyperthyroidism is markedly reduced or cured, it should be borne in mind that in such cases digitalis cannot reduce the action of the heart to a normal rate, and if large doses are used a toxic condition may be induced. On the other hand, if the generally effective doses are given the heart action will be somewhat reduced, and to that extent the myocardium will be conserved. Thus, for example, in a case in which auricular fibrillation is present, and the ventricular rate is 150 to 160, absolute rest in bed may reduce the rate to from 130 to 140; digitalis may then cause a further reduction to from 110 to 120, and in many cases Lugol's solution will reduce the rate still further. It would seem that the more pronounced the hyperthyroidism the less effective the digitalis; but if the hyperthyroidism is temporarily reduced by the use of Lugol's solution, then the effect of the digitalis is increased. Patients will usually tolerate 40 minims of a standard tincture daily over a long period without the development of any toxic symptoms. Unless it is especially indicated, it is best to give Lugol's solution only before operation, but after the patient has entered the hospital.

The preoperative requirement is of such importance in these cases that it seems worth while to give here a rather complete outline of the salient features: (1) Absolute rest in bed. (2) Simple diet of high caloric value. (3) Daily fluid intake, 3000 cc.

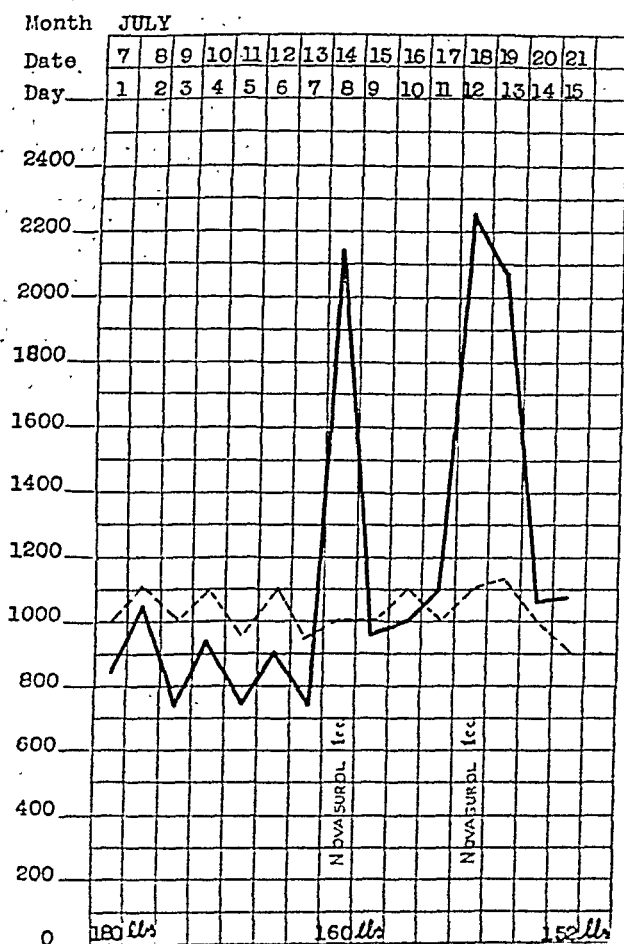
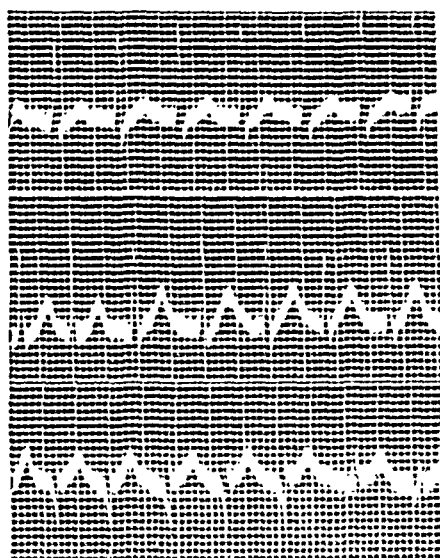
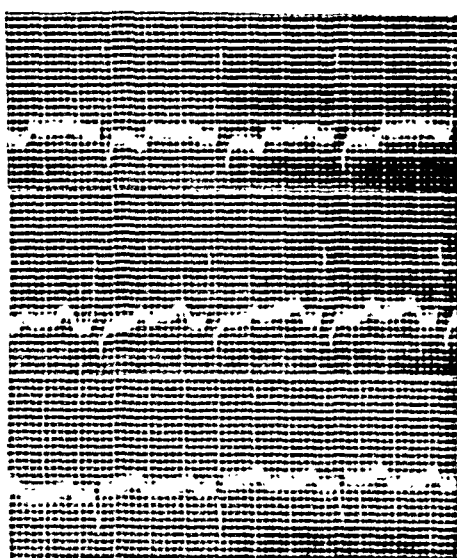


FIG. 1.—Effect of novasurol on the urinary output in a case of hyperthyroidism associated with auricular fibrillation, marked cardiac decompensation, edema and ascites. The heavy, continuous line represents the urine output, the broken line the water intake. Note that between July 7 and July 28 the patient lost 28 pounds in weight. On the latter date she had no edema, the ascites had disappeared and she was ready for operation.

(4) Iugol's solution, 15 minims, three times daily. (5) Tincture of digitalis, 2 cc. every four hours for six doses. (6) Sedatives, luminal or bromids as preferred; morphin may be indicated in cases of marked restlessness or insomnia. (7) If signs of heart failure are

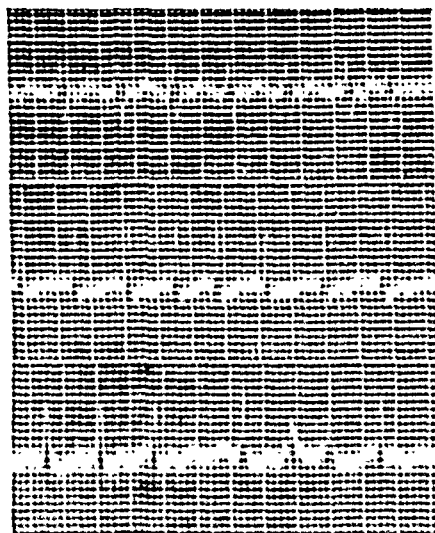


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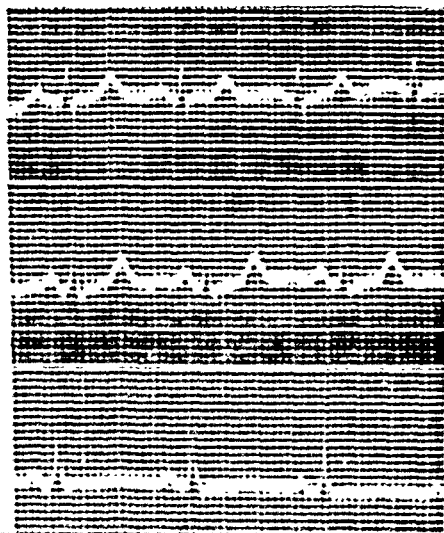


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FIG. 2.—Electrocardiographic tracings in a case of auricular fibrillation associated with hyperthyroidism. *A*, characteristic tracing of auricular fibrillation; *B*, normal tracing after operation.



A



B

FIG. 3.—Electrocardiographic tracings in a case of auricular fibrillation associated with hyperthyroidism.

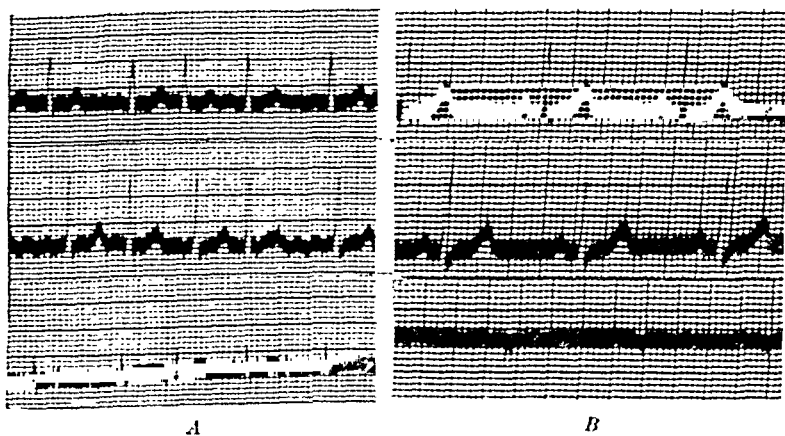


FIG. 4.—Electrocardiographic tracings in a case of auricular fibrillation associated with hyperthyroidism.

present the daily fluid intake should be reduced to 1000 cc., and more digitalis should be administered. If auricular fibrillation is present then a regular daily dosage of digitalis should be given, the amount to be determined by the circumstances in the individual case. Usually 20 minims, three times a day is sufficient. (8) If anasarca or edema is present the following measures should be employed: (a) ammonium chlorid, 15 gr., four times a day for two days before using novasurol, and throughout the period of treatment with novasurol; (b) novasurol, intravenously, from 0.5 to 1 cc., every three or four days (Fig. 1).

The above preoperative regimen is making it possible in many cases to eliminate ligation and to make the resection or partial resection the primary operation. This appears to be chiefly due to the use of Lugol's solution.

It cannot be emphasized too strongly, however, that Lugol's solution should not be used until it is certain that the patient is to be operated upon, as the later effect of this medication appears to be a progressive aggravation of the hyperthyroidism, which follows whether the use of Lugol's solution be continued or discontinued. This observation, however, should not contraindicate the use of Lugol's solution in those cases in which the prognosis is otherwise hopeless, as it may bring about enough immediate improvement to allow the operation to be performed.

Case Reports. The following cases have been selected as illustrating the outstanding characteristics of these cases and the progress which may be expected:

CASE I.—(156407.) A married woman, aged forty-five years, came to the Clinic complaining of shortness of breath and rapid pounding of the heart. The personal history revealed the fact that these symptoms had gradually increased since they were first experienced five years before. The patient had been treated for heart trouble with some resultant improvement, but four months before she had had a recurrence of the heart symptoms together with nervousness, loss of weight and cough. At that time she was in bed for four weeks, but suffered from dyspnea so much that she could not lie down. Her appetite was good; her digestion and bowel action were normal.

Physical examination revealed a woman who looked chronically ill and was perspiring freely. She weighed 185 pounds, her usual weight being 200 pounds. Blood pressure, 120 systolic and 76 diastolic; heart rate, 170; pulse rate, 120. There was no exophthalmos or lagging of the eyelids. Only a slight enlargement of the thyroid could be palpated, but the right lobe felt nodular. The heart was enlarged to the left, extending just beyond the nipple line. The rhythm was completely irregular with a pulse deficiency of 50. There was a systolic murmur at the apex which was transmitted to the axilla. There were no other murmurs. There was impaired resonance of the base of the right lung with diminished breath sounds but no râles. The liver extended two fingers' breadth below the costal margin. There was some edema of the legs.

Urine examination: Acid; specific gravity, 1020; albumin, 2+; a few coarse and a few fine granular casts; no sugar.

Basal metabolic rate: +33 per cent.

Roentgen ray examination of the chest showed an enlarged heart, together with pneumocardiac fibrosis.

Electrocardiographic examination gave the characteristic tracing of auricular fibrillation.

Diagnosis: Small adenomatous goiter with auricular fibrillation and heart failure.

Treatment: Absolute rest in bed. Digitalis, 30 minims, every four hours for 6 doses, followed by 20 minims, four times daily, for twelve days. At the end of this period the heart rate was reduced to from 110 to 120, with a pulse rate of from 100 to 110. Lugol's solution, 10 minims, three times a day, was then given for fifteen days, at the end of which period the heart rate was reduced to approximately 100 and the pulse deficit had disappeared, as had also the signs of heart failure. Seven days after the administration of Lugol's solution had been discontinued a lobectomy was done, part of the right lobe and of the isthmus being removed. As the heart rate increased to 180 during the operation, none of the left lobe was removed.

Pathologic diagnosis and report: Colloid adenoma. Macroscopic examination: One lobe of the thyroid, weighing 30 gm., presenting a fairly firm cut surface and containing, in the lower pole, a well-encapsulated colloid-appearing adenoma of the size of a walnut. Microscopic sections through both the adenoma and the bulk of the gland show small and large acini lined by flattened cuboidal epithelium. The lumina contain colloid material.

Postoperative course: There were no postoperative complications, and the patient left the hospital on the eighth day. As the auricular fibrillation persisted, however, she reentered the hospital. Five grains of quinidin were given, three times a day for three days, without any effect on the heart rhythm. It was not considered advisable to give any more quinidin, and the patient was allowed to return home. One month later the auricular fibrillation suddenly ceased.

CASE II.—(154690.) A married man, aged thirty-nine years, came to the Clinic complaining of nervousness, rapid heart, tremor and loss of weight. These symptoms had first developed five years before. Two partial thyroidectomies performed elsewhere respectively two years and one year before were each followed by temporary improvement. The action of the heart had been persistently irregular during the preceding four years. Three weeks before he came to the Clinic there had been an acute recurrence of the symptoms accompanied by rapid loss of weight, sweating and attacks of nausea and vomiting.

Physical examination: The patient was 6 feet in height and weighed 161 pounds, his usual weight being 190 pounds. Blood pressure was 180 systolic and 90 diastolic; heart rate, 160; pulse rate, 108. Marked exophthalmos was present with fibrillary tremor of the tongue and marked tremor of the hands. A large mass of thyroid tissue still remained which on palpation felt smooth, firm and rubbery. No thrills were felt. The heart was enlarged 2.5 cm. to the left of the nipple line at the sixth interspace; there was a systolic murmur at the apex which was transmitted to the axilla, and there was a soft murmur in the pulmonary area; the rhythm was completely irregular. The lungs were clear. The liver was not palpable. There was no edema.

Urine examination: Albumin, 1+; no sugar; numerous pus cells; fairly numerous hyalin casts.

Electrocardiographic examination gave the typical tracing of auricular fibrillation (Fig. 2A).

Diagnosis: Recurrent hyperthyroidism and auricular fibrillation.

Treatment: The patient entered the hospital and was given 15 minims of Lugol's solution, three times a day, and 2 cc. of tincture of digitalis, every four hours for six doses. On the fifth day part of the remainder of the right lobe and of the isthmus of the thyroid were removed. The heart began to fibrillate rapidly so that none of the left lobe was removed.

Pathologic report: Macroscopic examination: A mass of thyroid tissue, weighing 30 gm., which on section presents a fairly compact surface traversed by dense bands of fibrous tissue. Microscopic examination: Fairly uniform and only slightly enlarged acini, lined for the most part with proliferating hyperplastic cuboidal epithelial cells which, however, do not show an extensive hyperplasia and have only a spare colloid content. One section shows fairly extensive fibrosis with scattered lymphoid follicles.

Pathologic diagnosis: Moderate hyperplasia of the thyroid.

Postoperative course: On account of the cardiac condition at the time of operation the wound was left open and a moderate hemorrhage occurred, but otherwise the postoperative course was uneventful, and the patient left the hospital thirteen days after the operation. He returned nine months later, showing marked improvement. The eyes were still prominent, but there were no tremors. There was a slight palpable enlargement of the lobe of the thyroid. The heart was enlarged to just beyond the nipple line. The heart rate was 116; pulse rate, 116; blood pressure, 125 systolic and 80 diastolic. There was a faint systolic murmur at the apex and the heart rhythm was irregular. The lungs were clear. The liver was not palpable. There was no edema. Basal metabolic rate, +37 per cent. It was considered advisable to remove part of the left lobe of the thyroid. Upon admission to the hospital the patient was given 15 minims of Lugol's solution, three times a day, for six doses, and 30 minims of tincture of digitalis, every two hours for six doses, followed by 30 minims, three times a day. On the thirteenth day 45 gm. of tissue were removed from the left lobe, which had extended slightly below the sternum. This tissue showed more of a colloidal appearance on the cut surface than was the case with that removed at the preceding operation and the sections showed the acini to be lined by well-developed cuboidal cells, with only an occasional slight proliferation. All the acini contained colloid and the tissue was interspersed with lymphoid follicles.

Second postoperative course: The postoperative course was uneventful, although the auricular fibrillation persisted. The patient left the hospital on the seventeenth day, and five days later was given 1 dose of 5 gr. of quinidin, after which the heart action became regular and has remained so to date. There has been no evidence of any recurrence of hyperthyroidism.

CASE III.—(157203.) A married woman, aged thirty-seven years, came to the Clinic complaining of nervousness and weakness, rapid heart rate and shortness of breath. She had a very bad cough and stated that she occasionally coughed up a fragment of mucus. Fifteen months before she had had a "nervous breakdown," after which she began to lose weight and noted an increased heart rate on exertion or when excited, together with dyspnea at times. During the previous winter she had had two or three attacks of tonsillitis and six months before she came to the Clinic she had rheumatism in the legs which later occasionally became swollen, the swelling disappearing when she went to bed. For the preceding six weeks she had raised a considerable amount of mucus but never any blood. About a year before she had first noticed an enlargement of the thyroid gland and at that time she took some iodine tablets, applied some iodine salve to her neck and began the use of iodized salt which she had continued to use. For two weeks during the preceding months she had been in the hospital

on account of dropsy from the waist down. For the preceding three or four weeks she had had some headaches but no vomiting or nausea. She had noticed some increase in prominence of the eyes.

Physical examination: The patient weighed 103 pounds, her normal weight being 115 pounds. Heart and pulse rate, 136; blood pressure, 115 systolic and 90 diastolic. Palpation revealed diffuse enlargement of the thyroid gland, with marked pulsation in the vessels and thrill over both poles. The heart was enlarged. In the sixth interspace was a loud systolic murmur, which was transmitted to the axilla. Auscultation of the lungs revealed dullness and distant breath sounds in the right apex. After her admission to the hospital 100 cc. of straw-colored fluid was withdrawn from the pleural cavity, examination of which betrayed the presence of no organisms; albumin, 23 per cent. Differential cell count: Polymorphonuclears, 18 per cent; large mononuclears, 5 per cent; lymphocytes, 77 per cent. Abdominal examination showed the presence of ascites and the ankles and legs were markedly edematous.

The urine showed a moderate trace of albumin; one to six pus cells per high power field, a few fine and a few coarse granular casts and many shreds of mucus. The kidney functional test was normal. A cystoscopic examination showed a mild trigonitis and a condition suggestive of cystitis.

Electrocardiographic examination gave the typical tracing of auricular fibrillation (Fig. 3).

Diagnosis. Hyperthyroidism, cardiac decompensation, auricular fibrillation.

Treatment. The patient entered the hospital and was given 2 cc. of digitalis every four hours for 6 doses. On account of the condition of the heart and lungs, and the presence of ascites, the patient was kept under treatment with digitalis, quinidin and sedatives for three weeks, when ligations were done on two successive days. Three months after the ligation, when she reentered the hospital for thyroidectomy, she had gained 37 pounds in weight, the blood pressure was 130 systolic and 80 diastolic and she had a pulse rate of from 90 to 104. A faint systolic murmur could still be heard but no cardiac disturbances were found on electrocardiographic examination, and the patient reported that she had had no subjective symptoms referable to the heart.

Pathologic diagnosis: Colloid goiter. Macroscopic examination: The thyroid gland weighed 165 gm.; the lobes equal in size. On section, fairly firm but rather colloid-appearing cut surface. Microscopic examination: Sections through the gland show it to be composed of rather small acini lined by single layers of compressed cuboidal epithelial cells. All the acini contain colloid material and are interspersed with normal lymphoid follicles.

When last seen, five months after this operation, the patient was entirely free from all symptoms referable to the heart or thyroid. She still had some urinary disturbance for which appropriate treatment was prescribed. This case is of special interest because of the disappearance of the cardiac symptoms after the ligations and before the thyroidectomy.

CASE IV.—(134584.) A married woman, aged forty-one years, came to the Clinic complaining of palpitation which had been present ever since an attack of diphtheria eight years before. During the preceding six months she had lost some weight. Her appetite was good, she was not especially nervous, did not tire easily and did not perspire excessively. She had a goiter which had been present for ten years but was not enlarging.

Physical examination: The patient weighed 110 pounds. On palpation the thyroid was small but firm and rubbery, and the right lobe felt nodular. The palpebral fissures were widened. There was a slight

digital tremor. Pulse rate, 108; blood pressure, 128 systolic and 80 diastolic. Examination of the heart showed no thrills; border, 3.75 cm. to the right and 9.75 cm. to the left of midsternum; rhythm completely irregular; a faint mitral systolic murmur; no basal râles; liver not palpable. Slight edema of the legs. (Varicose veins and thrombophlebitis had followed an attack of typhoid fever at the age of nineteen years.)

Electrocardiographic examination gave the characteristic tracing of auricular fibrillation (Fig. 4).

Basal metabolic rate, + 66 per cent.

Urinalysis gave no abnormal finding except for a trace of albumin.

Diagnosis. Adenomatous goiter with hyperthyroidism, myocardial degeneration, and auricular fibrillation.

Treatment: A ligation of the right superior thyroid artery was performed, three months after which the patient reentered the hospital for thyroidectomy, which was performed on the third day after preliminary treatment with digitalis, 2 cc., every four hours, and thyroid extract, 2 gr., twice a day. Both lobes and the isthmus were removed. Convalescence was uneventful and the patient left the hospital on the sixth day after operation.

Pathologic report: Macroscopic examination: A mass of thyroid tissue the size of a duck's egg, the cut surface of which shows colloid, within which is a follicular adenoma the size of a pigeon's egg. Microscopic examination: Section through the adenoma contains small acini, lined with cuboidal epithelium, which in some areas shows proliferation; practically all the acini contain colloid. Sections through remaining tissue show only typical colloid appearance.

Pathologic diagnosis. Follicular adenoma in colloid goiter with moderate hyperplasia.

Postoperative course: The patient reported that the heart action became regular about two weeks after leaving the hospital. An electrocardiogram, taken five months after the operation, showed that the rhythm was regular. A year and ten months after her operation the patient reported that her heart had remained regular until two months before this time. She had been under treatment for a varicose ulcer, for which hyperdermic injections of iron, arsenic and strychnin had been given, together with iodine by mouth. After two weeks of this treatment the right lobe of the thyroid enlarged suddenly and became sore, and there were attacks of rapid irregular heart action. Both of these symptoms subsided promptly when the iodine therapy was discontinued. At the time of this last visit the heart rhythm was regular and there was a systolic murmur at the apex, slight fullness of the right lobe of the thyroid, together with the varicose ulcer of the left leg but no symptoms referable to the heart or goiter.

Summary. The occurrence of cardiac disturbance does not appear to depend upon the pathologic type of goiter, whether it be diffuse hyperplastic goiter, fetal adenomatous goiter or colloid goiter with adenomatous nodules; but it seems rather to depend entirely on the presence of hyperthyroidism. Cardiac disturbance is most frequently associated, however, with colloid goiter with adenomatous nodules and is found most frequently in individuals over forty-five years of age in whom some degree of arteriosclerosis is already present, this of itself making them more readily subject to cardiac complications.

In some cases thyroid adenomata and adenomatous goiters appear

to cause cardiac damage, at times even before signs of hyperthyroidism become manifest and before the basal metabolic rate has become elevated to a level which would indicate the presence of hyperthyroidism.

There are some cases in which, according to the history, goiter has been present for many years and there have been recurrent spells of nervousness, some loss of weight and palpitation, especially following colds, etc. In these cases the patient was never obliged to stop work or go to bed until the heart rhythm suddenly changed to auricular fibrillation. This change occurs without any sudden increase in the hyperthyroidism, and it seems as if the damage to the heart must be the result of a long-continued mild irritation or stimulation.

It is of the utmost importance that the cardiac condition be recognized early in order that radical treatment may be instituted before serious heart damage has taken place.

Conclusions. 1. In cases of auricular fibrillation associated with hyperthyroidism in which the former condition is of recent onset the heart action usually becomes regular after thyroidectomy, or, if not, the use of quinidin will usually suffice to cause the restoration of the normal rhythm.

2. In cases in which auricular fibrillation of long standing is associated with hyperthyroidism of recent onset thyroidectomy is well borne; although the heart action seldom is restored to a normal rhythm, the heart rate can be controlled by digitalis and the condition of the patient will be much improved.

3. Cases of hyperthyroidism, in which a grave degree of heart failure is present, and in which a regimen of absolute rest, digitalis and Lugol's solution does not suffice to clear up the condition of the heart, are always desperate risks and a considerable mortality is inevitable. In these cases, however, the prognosis without operation is so hopeless that operation should be performed if there is the slightest hope of its being successful.

4. In all cases of hyperthyroidism the preoperative use of digitalis and of Lugol's solution for at least a week prior to operation is advisable.

5. In all cases of hyperthyroidism it is of special importance that the operation be performed before the onset of fibrillation or of heart failure.

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AGRANULOCYTIC ANGINA.

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SCHULTZ,²² in 1922, brought to our attention a group of cases with severe gangrenous stomatitis and unusual blood picture occurring in women of middle age with negative past histories. The onset was acute with fever, chills and malaise. The tonsillar region and pharynx became injected and necrotic. There was local lymph node enlargement. Jaundice was present but there was no evidence of cutaneous hemorrhage. The liver and spleen were enlarged in one-half the number. On examination of the blood, the red blood cells, hemoglobin and blood platelets were normal. The white blood corpuscles were greatly reduced in number and on differential count the polymorphonuclear leukocytes were decreased or were absent, the lymphocytes were relatively increased up to 100 per cent. All cases died in three to four days of pneumonia. At autopsy, the bone marrow was grossly red in color while on microscopic examination it was cell poor with almost complete absence of granulocytic cells. Because of the peculiar damage to the granulocytic blood cells associated with stomatitis, Schultz attached the name agranulocytic angina.

Following the initial report, similar cases were reported chiefly by the German writers. Leon¹¹ attempted to establish the condition as a previously undescribed clinical entity because of the blood appearance occurring in females, the presence of jaundice, the absence of hemorrhagic diathesis and septic foci, and lack of evidence of leukemia. Other authors cited conditions which might produce similar blood changes with stomatitis, mainly acute leukemia and certain cases of sepsis.

As more cases were analyzed the clinical and necropsy findings which earlier were thought to be constant, were found to vary in their presence and intensity. The extent of ulceration and the presence of hemorrhage was found to vary. Lauter¹⁰ was the first to report a case resulting in recovery. Rotter²¹ reported the first case in a male patient. During the last two years, more cases have been reported and the clinical and pathologic records have given data from which it will be possible to obtain a broader conception of the disease process.

Two cases of the agranulocytic type have recently come to autopsy at the Toronto General Hospital. The following is a protocol of the hospital records:

Case Reports. CASE I.—C. B., 36442, female, aged twenty-four years, married. Previous to 1923 the patient was never ill. For the past two years she had been under treatment for syphilis at the out-patient depart-

ment, her husband being treated at the same time. The blood Wassermann was strongly positive. A slight cervical discharge present for two years was never positive for gonococcus. Physical examination was always negative. On March 11, 1924, while feeling well, the patient received the sixth of a series of intravenous neodiarsenol injections, on March 18, she complained of sore throat. During the following few days she noticed a swelling at the left side of the neck and felt feverish. She thought her skin was yellow, had no appetite, bled slightly from the nose, coughed a blood-tinged sputum but had no chill. She was admitted to the hospital on the service of Prof. Duncan Graham.

Physical Examination. The patient was poorly developed and nourished. The skin was of a sallow color but not jaundiced. Pectoral oris was marked, the oral hygiene was bad. Discoloration and hemorrhage were seen about the gum margin of two teeth. The tongue was slightly coated but moist. An area of ulceration was on the buccal mucous membrane opposite the last right molar teeth. The throat was inflamed, the tonsils were not enlarged. Clotted blood was in both nostrils. The anterior and posterior cervical lymph nodes were palpable. Slight impairment of resonance was found anteriorly at the apex of the right lung. The cardiac and abdominal examinations were negative. There were no cutaneous hemorrhages. The reflexes were all present and normal. Temperature, 101° F.; pulse, 100 to 130; respirations, 24.

Laboratory Examination. Blood: Red blood cells, 4,000,000 per cm.; hemoglobin, 64 per cent; white blood cells, 2500 cm.; differential blood count (300 cells), polymorphonuclear leukocytes, 6 per cent; eosinophils, 2 per cent; lymphocytes, 74 per cent (56 per cent large); endothelial cells, 18 per cent. The leukocytes had well-stained granules; the nuclei of the lymphocytes were rarely irregular. The endothelial cells were sometimes irregular in shape, few had bilobed nuclei. The red blood corpuscles were normal. Oxidase stain of the blood smear showed no granules outside the leukocytes and eosinophils. Van den Bergh of the blood—direct and indirect negative. Bleeding time, twenty-five minutes; clotting time, seven minutes. Urine, occasional cast and white blood cell; Diazo reaction, negative; urobilin, negative; occult blood, negative; throat culture, negative for *Bacillus diphtheriae*; streptococcus hemolyticus predominating. *Bacillus fusiformis* and spirochetes were present. Blood culture, sterile.

Course of disease. The temperature fluctuated between 101° and 105° F. The white blood count fell progressively, on the second day being 1100 per cm. On the fourth day purpuric spots appeared on the left forearm. The sorethroat was more severe, the mouth ulceration extended. Hemoglobin, 55 per cent; white blood cells, 800 per cm. The following day purpuric spots were seen on the soft palate. The left tonsil was sloughing, there was no surrounding inflammatory reaction. Red blood cells, 3,500,000 per cm.; white blood cells, 540 per cm. Microscopic examination of the tonsillar exudate showed a fibrinous bloodclot containing many bacteria, a few endothelial cells and polymorphonuclear leukocytes. On the sixth day, a friction rub developed at the base of the left chest. The general condition was worse. Much blood was in the sputum, occult blood positive in the stool. White blood cells, 520 per cm. On the seventh day, moisture and impairment or resonance were increased in the left chest. The patient died on the eighth day in the hospital.

Clinical Diagnosis. (1) Acute lymphatic leukemia; (2) cancerum oris; (3) purpura hemorrhagica.

Autopsy (25/58) was performed twelve hours after death by Dr. J. Edgar Bates. The skin had a slightly yellowish though not icteric tinge. A few petechial spots were scattered over the neck, upper thorax, arms and abdomen. The teeth were dirty, the gums dark in color and covered by clotted blood. The gum margin of both upper and lower jaw had a

purplish border 4 mm. in width with a few yellowish soft necrotic areas and with no adjoining hyperemia. Clotted blood was found at the vaginal orifice.

In the mediastinum a few soft and succulent lymph nodes measured 0.75 cm. in diameter. A number of large hemorrhagic collections were beneath the pericardium of the right ventricle and beneath the endocardium. The muscle and valves of the heart were normal. The aorta presented a few superficial fatty streakings on the posterior wall. Petechial hemorrhages were found beneath the pleura of all lung surfaces. The lower lobes of both lungs were covered by a fibrinous exudate, were dark-red in color, nonrepitant and firm. On section of the lungs many small, dry, grayish-red areas 1 to 1.5 cm. in diameter stood out on the dark surface.

Abdomen: A few petechial spots were found on the parietal peritoneum while small collections of blood were retroperitoneal. At the head of the pancreas a few of the lymph nodes were large, soft and red in color. The gastrointestinal mucous membranes were injected. There were petechial hemorrhages in the mucosa of the stomach, ileum and cecum. The intestines contained a considerable amount of dark-red fluid. The liver and kidneys showed a degree of cloudy swelling. Numbers of petechial hemorrhages were in the tissues of the right kidney. The pelvis of the kidney was filled with bloodclot. The spleen was large, flabby, and on section was a purplish-pink color with an increased amount of pulp and quite prominent Malpighian corpuscles. The bone marrow of the lower one-third of the right femur was reddish-yellow in color. The marrow of the lumbar vertebrae was fatty. The adrenal glands, gall bladder, urinary bladder, uterus, ovaries and Fallopian tubes showed nothing of note.

Microscopic Examination. The sections of lung presented an unusual appearance. The alveolar spaces of the consolidated portions were completely filled with a fibrinous and hemorrhagic exudate with little or no inflammatory cell reaction. The fibrin formed a compact network of fine threads and granules often more dense at the edges of the alveoli. Within the network were varying numbers of red blood cells but no polymorphonuclear leukocytes. Occasional endothelial cells and lymphocytes were deposited at the edges of the plugs of fibrin. This picture passed into adjoining areas where the alveoli were incompletely filled with serum, red blood cells, fibrin strands and endothelial cells, but rarely leukocytes. In the phosphotungstic acid hematoxylin stain the fibrin formed distinctive blue masses.

Spleen: The Malpighian follicles were small and quite sharply demarcated from the surrounding pulp. The cells of the follicles were uniformly quite mature with no abnormal forms. In the pulp the reticuloendothelial cells were most prominent and greatly outnumbered the lymphocytes. The endothelial cells showed variation in size and shape, the common cell having a rounded, roughly granular, pale nucleus in a pale cytoplasm. Mitoses were seen and a few cells with vacuolated cytoplasm contained phagocytosed particles. There were a few cells of the plasma type, but no polymorphonuclear leukocytes in the sections.

Lymph node from the region of the head of the pancreas. The lymphoid tissue was decreased and replaced by a reticuloendothelial cell hyperplasia. The germinal centers were small and composed of mature uniform lymphocytes. The reticuloendothelial cells of the pulp varied in staining and shape. Lymphocytes together with a few plasma cells filled the sinusoids. Occasional eosinophils were seen, but no neutrophilic leukocytes.

Bone marrow: The fat cell structure was maintained with a marked reduction in the number of blood cells. Medium-sized lymphocytes quite uniform in shape were most numerous. There were numbers of large cells with relatively large, coarsely granular, pale nuclei and pale, clear or vacuolated cytoplasm, which were considered to be reticuloendothelial

cells. A few of these were irregular due to mitotic changes. Myelocytes and eosinophils were seldom seen, neutrophilic polymorphonuclear leukocytes were absent. The red blood cell germinal centers and megakaryocytes appeared normal.

The heart, liver and kidneys showed a mild degree of cloudy swelling. In the liver there was no evidence of lymphoid cell increase. A few very small lymphocytic and endothelial cell collections, with an occasional eosinophil, were seen about the large vessels and glomeruli in the kidney. The loculated submucous hemorrhages of the intestine had no surrounding cellular infiltration. The gall bladder, pancreas, adrenal glands and ovaries showed nothing of note.

Autopsy Bacteriology (Dr. G. C. Cameron) Heart blood, *Bacillus acidilactici*; bile, no growth; spleen, *Bacillus lactis aerogenes*; uterus, *Streptococcus viridans* or pneumococcus (these failed to subculture).

Anatomical Diagnosis. (1) Acute gangrenous stomatitis. (2) Hemorrhage from mucous membranes of mouth, stomach, intestines and kidney. (3) Petechial hemorrhages of skin, epicardium, endocardium, pleura, peritoneum and pelvis of kidney. (4) Suffusion of blood into retroperitoneal tissues. (5) Hypoplasia of bone marrow. (6) Acute bronchopneumonia (confluent). (7) Acute fibrinous pleurisy. (8) Edema of lungs. (9) Cloudy swelling of liver, kidney and heart. (10) Acute splenitis with enlargement. (11) Superficial fatty streaks of aorta. (12) Syphilis.

CASE II.—N. S., 24881, male, aged thirty-eight years, service of Dr. Fulton Risdon. Six months previous to admission the patient, because of albuminuria, failed to pass the physical examination of a life insurance company. At that time he felt well and had no complaint up to the time of the present illness. One week before admission to the hospital the patient had malaise, weakness, sore throat and sore gums. The symptoms were progressive and soon led to prostration. On admission a history could not be elicited.

Physical Examination. The patient was a fairly well-developed adult male who was acutely ill and prostrate. Fetor oris was marked. The gum margins were gangrenous with quite a sharp demarcation from the more healthy tissues. The tonsils and pharynx were quite free. The cervical lymph glands, spleen and liver were palpable. Temperature, 101° to 104° F.; pulse, 120; respirations, 24.

Laboratory Examination. Red blood cells, 5,200,000 per cm.; hemoglobin, 82 per cent; white blood cells, 1200 per cm. Differential blood count: Polymorphonuclear leukocytes, 0 per cent; eosinophils, 2 per cent; lymphocytes, 76 per cent (73 per cent large); endothelial cells, 10 per cent; questionable or destroyed cells, 12 per cent. Difficulty was encountered in distinguishing between the large lymphocytes and endothelial cells. By the oxydase stain no myeloid or neutrophilic cells could be demonstrated. An occasional endothelial cell contained a few oxydase granules. The red blood corpuscles were normal. Urine—albumin positive, few white blood cells on microscopic examination. Direct smear from the mouth showed spirochetes not characteristic of the Vincent type. Throat culture—negative for Klebs-Loeffler bacillus, hemolytic streptococcus present. Blood culture contaminated by *Staphylococcus aureus*. Widal, negative.

Clinical Course of Disease. The patient's condition became steadily worse with intense toxemia and coma. On the second day the white blood cells were 1100 per cm. The following day intravenous neoarsphenamin 0.3 gm. was given. The patient, then in a terminal state, died one hour later.

Clinical Diagnosis. Aleukemic leukemia.

Autopsy (25259) was performed six hours after death by Dr. J. Edgar Bates. On external examination there were no cutaneous hemorrhages.

Sordes were on the lips. The teeth were loose, the gums necrotic. The gangrenous portion of the gums was black in color, friable and sharply margined from the neighboring more healthy mucous membrane. The surface of the hard palate was swollen and edematous with a few ulcerated areas on the right side. The cervical lymph nodes were palpable at the angles of the jaw.

The lobes of both lungs were matted together with old fibrous adhesions. Small petechial hemorrhages were beneath the pleura of the left lung; there was no consolidation. The heart was large with a relatively large left ventricle. The entire pericardium was covered by remnants of fibrous adhesions. A row of pinkish granular excrescences was found along the line of closure of the mitral valve. The other valves and endocardium were free. The aorta showed only a few yellowish streakings on the posterior wall.

Abdomen: The walls of the intestinal tract were edematous. Petechial hemorrhages were seen throughout the mucosa of the stomach and in the lower ileum. The liver was large and attached to the diaphragm by firm fibrous adhesions. The cut surface bulged and was finely dimpled by depression of the portal areas. The spleen was large, weighing 580 gm., and was also bound down by adhesions. On gross section, the purplish-red pulp was scraped away with difficulty, the Malpighian corpuseles could not be distinguished. Both kidneys were large, the cortical cut surface bulged and showed little distinction from the reddish-gray medulla. A caseous grayish area 2 mm. in diameter, sharply demarcated, was found in the cortex of the left kidney. The walls of the kidney pelvis were congested and spotted by petechial hemorrhages.

Microscopic Examination. In the sections of the ulcers of the mouth the gangrenous superficial tissues extended varying depths to the muscle layer, having a sharp margin bordered by edematous tissues. Many clumps of bacteria were lodged along the necrotic ulcer edge and by Levaditi's stain there were demonstrated many spirochetes of the bifidus type with some coarse bacillary forms in the same region. Beyond the necrosis there was no inflammatory cell reaction except an occasional lymphocyte, endothelial and plasma cell. These cells formed no particular zones of reaction. There were no polymorphonuclear leukocytes.

Heart: The heart muscle was normal. In the section of the mitral valve the endothelial covering near the valve tip was destroyed and a fungating fibrinous necrotic mass was attached to the surface. A few endothelial cells and lymphocytes with an occasional polymorphonuclear leukocyte were collected at the base of the necrosis and beneath the neighboring endothelium. The underlying tissues appeared hyaline-like, the capillaries were irregularly thick-walled, congested, and had few cells about them.

In the spleen, the Malpighian corpuseles were small, composed mainly of large, somewhat irregular-shaped lymphocytes. The lymph node germinal centers were quite small and not easily distinguished while the pulp varied in appearance. In some areas large lymphocytes with some irregularity in nuclear form were most prominent; in other areas a reticuloendothelial cell hyperplasia replaced the lymphoid tissues. The endothelial cells varied in shape, size and staining, some showed phagocytosis of cellular debris.

Kidney: Small groups of lymphocytes and endothelial cells were seen about local areas of fibrosis which involved the subcapsular tissues, glomerular tufts and tubules. Similar cells were infiltrated in well-demarcated areas into the peripelvic fat or about a few bloodvessels. No polymorphonuclear leukocytes were seen. The gray area described in the left kidney was a caseous necrotic area with foreign-body giant cells and surrounding lymphocytes and endothelial cells.

Bone marrow: The adipose cell structure contained few blood cells. The white-cell elements were made up almost entirely of lymphoid and endothelial cells. No definite mitoses were demonstrable. By oxydase stain, a few endothelial cells showed oxydase granules. There were no myeloblasts, myelocytes or polymorphonuclear leukocytes.

The fibrous stroma of the prostate gland was increased and many lymphocytes were collected beneath the acinar epithelium. The liver showed a mild degree of cloudy swelling with no cellular increase. The lung, gall bladder, pancreas and adrenal glands were not unusual.

Autopsy bacteriology was carried out by Dr. G. C. Cameron. Bile, no growth.

Anatomical Diagnosis. (1) Acute gangrenous stomatitis; (2) acute lymphadenitis (cervical); (3) acute verrucous mitral endocarditis; (4) petechial hemorrhages of pericardium, pleura, stomach, small intestine and pelvis of kidney; (5) obsolete tuberculosis of pleura; (6) dilatation of heart; (7) acute splenitis with enlargement; (8) chronic interstitial nephritis; (9) tuberculosis of kidney; (10) chronic prostatitis; (11) hypoplasia of bone marrow.

Résumé of both Cases. The two cases, one in a female, the second in a male, were admitted to the hospital with well-established changes and were studied only during the manifest stage of disease. The onset was with malaise, sore throat, weakness and high fever. The gangrenous stomatitis was extensive and associated with regional adenopathy. Both had no definite jaundice. Cultures from the mouth were negative for *Bacillus diphtheriae* and positive for hemolytic streptococcus. Both also revealed spirochetes, one of the Vincent type on culture, the other a bifidus-like organism on section. The blood pictures coincided, with leukopenia, decrease in the polymorphonuclear leukocytes, a relative lymphocytosis and increase in the endothelial cells.

At autopsy, the bone marrow which in the gross appeared red, on microscopic examination was cell-poor with almost total absence of granulocytic cells and a predominance of lymphocytes and endothelial cells. Endothelial hyperplasia was present in the spleen and lymph nodes. The regions of infection, the ulcers of the mouth, the heart valve lesion and the pneumonic process showed a peculiar lack of cellular response with no polymorphonuclear reaction. Petechial hemorrhage was noted as a late phenomenon in Case I. This case, which was serologically syphilitic, showed no anatomic lesion of syphilis at autopsy, while Case II which had given a history of albuminuria revealed a tuberculous focus in one kidney. A suggestion of lymphoid infiltration was seen in Case II in the kidney and possibly the lymph node.

Review of Literature. In a review of the literature on agranulocytic angina 43 cases were collected. The initial report was made by Schultz of 6 cases, which were later reviewed by Leon.¹¹ Since that time the following cases have been reported: Friedmann,³ 4; Bantz,^{2,3} 5; Lauter,¹⁰ 2; Elkeles,⁶ 2; Lovett,¹³ 1; Petri,¹⁸ 1; Skiles,²⁴ and Piette,²⁰ 1; Rotter,²¹ 6 (2 previously reported); Ehrmann and

Preuss,⁵ 1; Zadek,²⁸ 5; Moore and Wieder,¹⁷ 1; Pfab,¹⁹ 1; David,⁴ 1; Schultz and Jacobowitz,²³ 5; Feer,⁷ 2; Hunter,⁹ 1.*

Clinical data was present in all. Thirty-six cases came to autopsy. Many writers have failed to record minor data and percentage estimates of various features are not usually possible.

The sex and age incidence is shown in Table I.

TABLE I.—SEX AND AGE INCIDENCE.

(a) Sex:	
Total number of cases	43
Females	34 (78%)
Males	9 (22%)
(b) Age:	
Age variation of all cases, 18 to 74 (1 case 4½ years)	
Females, average age, 46	
Males, average age, 29	

The past histories were negative in 27 cases. Table II shows the previous illness of the remaining 16.

TABLE II.—HISTORY OF PREVIOUS ILLNESS.

	Cases.
Negative past histories	27
History of previous illness	16
Previous oral infection	7
Typhus	3
Tuberculosis	3
Syphilis	3
Pneumonia	3
Rheumatism	2
Anemia	2
Operations	3
Infections (cellulitis)	2
Kidney disease	2

The mode of onset in 28 of the cases was acute, coming in a period of good health. In the remaining 15 the acute manifestations of agranulocytic angina occurred after a protracted period of ill health or following a definite illness.

* References were found to a case reported by Pelnar, *Cas. Lek. Cesk.*, 1924, 83, 1398, which could not be obtained.

A case reported by Krumbhaar (*Leukemoid Blood Pictures in Various Clinical Conditions*, *Am. J. Med. Sci.*, 1926, 172, 519) has come to our attention since this paper was completed. A female, aged twenty-one years, with acute ulcerative stomatitis developed a leukopenia of 3500 following an initial leukocytosis. Although the polymorphonuclear leukocytes decreased to 0.5 per cent, myelocytes appeared up to 60 per cent, resulting in a decrease of over 50 per cent of the granulocytic series. When the normal granular cells again appeared in the blood stream, the abnormal granular elements disappeared. The blood picture was, therefore, never completely agranulocytic. The presence of the abnormal blood cells is suggestive either of an aleukemic type of leukemia, or, in view of the patient's recovery and return of the blood picture to normal, of the appearance of immature cells such as may be seen whenever the marrow is hard pressed.

TABLE III.—MODE OF ONSET OF DISEASE.

	Cases.
Acute onset, during good health	28
Acute onset, during period of ill-health	15
Malaise, 1 week to 5 months	5
Malaise with jaundice 3 weeks	1
Tonsillitis with recovery	1
Infections, purulent	2
Influenza	1
Tuberculous arthritis 1 month duration	1
Chronic arthritis, 5 months' duration	1
Fracture of tibia, 3 weeks' duration	1
Operations within 3 months' duration	2

The onset of disease was marked by high fever of 101° to 105° F., sore throat, general malaise and dysphagia. A state of exhaustion not infrequently was seen early in the disease, coma often preceded death. Jaundice occurred in 25 cases (58 per cent). Of this number, jaundice was the initial symptom in 1, was slight in 5, progressive in 3 and appeared late in 6 cases. The incidence of various symptoms is shown in Table IV.

TABLE IV.—SYMPTOMS AT ONSET.

	All cases
Fever	32
Sore throat	14
Malaise	10
Chills	25
Dysphagia	4
Headache	4
Muscle pains	5
Herpes	3
Vomiting	2
Bleeding from mucous membrane	25
Jaundice	

The oral cavity was involved in an inflammatory process in all cases. Ulceration and necrosis were most frequently seen. Necrosis involved in order of frequency the tonsil in 19; throat, 13; gums, 9; tongue, 6; larynx, 5; esophagus in 2 instances. A membrane was attached to the diseased surfaces in 25 cases. In 24 of these it involved the tonsils, in 13 it extended to adjoining areas. The membrane frequently was attached to nonulcerated areas. The necroses were described as being nonmarginated (Lovett¹³), with overhanging edge (Rotter²¹) or with no surrounding inflammatory reaction (Friedmann⁸ and Rotter²¹). On microscopic examination of the oral necrosis, the findings are noteworthy. In 4 cases (Lovett,¹³ Rotter²¹) there was no cellular reaction. In 12 others there was only slight lymphocytic, endothelial, and plasma cell reaction. Polymorphonuclear leukocytes deeply placed were seen in only 1 case (Bantz²). In 6 cases bacteria were infiltrated at the ulcer margin. Ulcerations outside of the mouth are indicated by Table V.

TABLE V.—LOCATION OF EXTRAORAL ULCERS.

	No. of cases.
Stomach—multiple small lesions	6
large ulcers	3
Duodenum	2
Ileum	6
Colon	5
Anus	4
Rectum	2
Cervix	2
Vagina	8
Symphysis	2
Hip	1
Conjunctiva	1

Cutaneous petechial hemorrhages or evidence of hemorrhagic diathesis were clinically noted in 8 cases while visceral petechial hemorrhages were found at autopsy in 12 cases. Large hemorrhages were seen in various organs; the bone marrow and lungs of 2 cases, retina in 1 and into the stomach and small intestine. The blood platelet count was recorded in 27 cases. It was normal in 20. The proportion of normal counts was higher in the absence of hemorrhagic diathesis. High and low counts, however, were seen with and without hemorrhages.

Regional lymph node enlargement was noted in 15 instances. This was occasionally unilateral and only twice associated with pain on pressure. (Elkeles,⁶ Petri¹⁸). At autopsy peribronchial, mesenteric and cervical glandular enlargements were found in 4 cases. (Rotter,²¹ Schultz and Jacobowitz²³). The microscopic picture of the lymph nodes reported by Lovett¹³ was of small hemorrhages while Rotter,²¹ Pfab¹⁹ and Petri¹⁸ noted endothelial-cell hyperplasia. Both the liver and spleen were enlarged in 7 cases (Schultz,²² Schultz and Jacobowitz,²³ Friedmann,⁸ Bantz,² Rotter²¹). The liver alone was enlarged in 5 (Lovett,¹³ Lauter,¹⁰ Ehrmann and Preuss,⁵ Friedmann,⁸ Feer⁷) and the spleen alone in 7 cases (Rotter,²¹ Zadek,²⁸ Schultz and Jacobowitz,²³ David,⁴ Bantz²). Evidence of lymphoid metaplasia was infrequently seen. Pfab¹⁹ noted lymphoid collections in liver, spleen, lymph nodes and bone marrow. Periportal lymphocytic collections were mentioned in 11 cases by 2 writers (Rotter,²¹ Schultz²²). Perivascular lymphocytic collections in the liver were seen seven times (Schultz²² and Pietti²⁰). Polymorphonuclear leukocytes were never seen in the liver. The spleens of 13 cases showed an endothelial-cell proliferation (Schultz,²² Schultz and Jacobowitz,²³ Rotter,²¹ Bantz,² Pfab¹⁹). Oxydase granules were seen in the cells of questionable origin in only 3 cases (Zadek,²⁸ Pfab¹⁹).

Cultures taken from the oral cavity showed no uniformity of organisms. Klebs-Loeffler bacilli were reported once by Schultz.²² Vincent's spirochetes were seen by Skiles²⁴ and Piette,²⁰ David,⁴ Bantz,² and Moore and Wieder.¹⁷ Pneumococcus was recorded by Schultz²² and Bantz,² *Bacillus pyocyaneus* by Lovett.¹³ Positive

blood cultures occurred in 9 cases; *Streptococcus hemolytic* (Lauter,¹⁰ Elkeles⁶), staphylococci (Schultz²² 2 cases, Schultz and Jacobowitz²³), *Bacillus pyocyaneus* (Friedmann⁸), *Bacillus coli* (Schultz and Jacobowitz²³). At autopsy the bacteriologic findings were also inconclusive.

The white blood cell count in 41 cases was reduced. The average count was 1200 cells per cubic millimeter, the lowest count was 100 per cubic millimeter. An initial leukocytosis was seen in two instances, the importance of which will be discussed later. During the course of disease the usual observation was a gradual decrease in the number of cells. The percentage of polymorphonuclear leukocytes was always reduced to an average between 0 and 6 per cent. A relative lymphocytosis was always noted, varying from 60 to 100 per cent. Endothelial cells were 4 to 8 per cent. In 7 cases premature lymphoid cells were seen on blood smear (Rotter,²¹ Petri,¹⁸ Zadek,²⁸ Lauter,¹⁰ Friedmann⁸).

The red blood cell counts were normal in 25 of the cases. In 10 cases there was no record, the remaining 8 showed a reduction in the number and changes in the red blood cells characteristic of a secondary type of anemia. Occasionally this anemia was progressive.

The bone marrow at autopsy was, in the gross, red in 27 of the cases examined. In 6 the marrow was "fatty." On microscopic examination, the most common observation was a cell-poor structure with great decrease or absence of the granulocytic elements. The lymphocytes on the contrary were prominent. Cells of the reticuloendothelial type with vacuolated, pale, clear cytoplasm and roundish, quite chromatin-free nuclei were increased in number. The red blood cell germinal centers were normal. Other lesions found at autopsy are shown in Table VI.

TABLE VI.—LESIONS FOUND AT AUTOPSY.

	Cases.
Pneumonia	9
Pachymeningitis hem. interna	3
Purulent otitis media (bilateral)	1
Endocarditis, acute	1
Pyelonephritis	1
Carcinoma of uterus	1
Intraperitoneal bleeding from ruptured Graafian follicle	1
Hypoplasia of aorta	1
Multiple anomalies	1

The disease resulted in death in 40 cases, there were 3 recoveries. The average duration of illness was four to eight days, the extremes two to forty-two days. It is interesting to note that Case III of Friedmann⁸ showed recovery from the gangrene of mouth and the blood picture but contracted pneumonia which resulted in death. The case of Moore and Wieder¹⁷ is the only one with record of recovery and subsequent death from a second attack.

Discussion. In agranulocytic angina characteristic changes are produced in the blood and blood-forming organs associated with gangrene and inflammation in various locations.

The decrease of polymorphonuclear leukocytes in the circulating blood is both relative and actual. This change could be produced by three means: increased peripheral blood destruction, abnormal distribution of cells or failure of cell development. The finding in the bone marrow of granular cell decrease at autopsy was significant. Zadek,²⁸ Schultz and Jacobowitz²³ in 3 cases removed bone marrow from the sternum during the height of disease. These specimens showed a cell-poor marrow with decrease in granulocytic elements, the same as was seen at autopsy. The hypoplasia of these granular cells is thus not a terminal event and the decrease of the cells in the blood stream appears to be due to failure of development of the cells in the bone marrow. The few cases, which have shown a fatty marrow in the gross, have little or no granular cell decrease. David⁴ has stated that in these the blood picture may be due to defect in cellular distribution and not to faulty cell formation.

The total number of lymphocytes, as was pointed out by Lovett,¹³ is reduced or remains normal, but the relative proportion is increased.

Reticuloendothelial cells are increased in the spleen, lymph nodes, bone marrow and in the circulating blood. These cells were distinguished with difficulty from many large lymphocytes and myeloblasts. The chief point of confusion was that few of the endothelial cells contained small oxydase granules. Hirschfeld, in discussion of Schultz²² first report, attributed the presence of these granules to degenerative changes. Recently McJunkin¹⁵ described a type of endothelial cell (mononuclears) arising from the spleen and bone marrow to contain few oxydase granules. The resemblance of the cells in the blood stream to those in the spleen and lymph nodes establishes them as of endothelial origin. Some endothelial cells are seen to be phagocytic and in the absence of the polymorphonuclear leukocytes remain as the chief combatants to infection.

The time relation between the appearance of the blood changes and of the mouth gangrene is of importance. Three cases were seen to develop acute disease in the hospital. These patients were admitted for: (1) Unexplained jaundice (Ehrmann and Preuss⁵); (2) tuberculous arthritis (Bantz³); (3) fracture of the tibia (Hunter⁹). The blood cell and differential counts on admission were normal. While under treatment, acute sore throat developed followed by ulcerative stomatitis. In each instance, changes were noted in the blood prior to the tissue changes. Lauter,¹⁰ in another case, observed that the height of the disease occurred on the day gangrene appeared in the mouth. In recovery of the latter case, the blood and clinical state improved simultaneously. The gangrene was quite rapid in healing while the blood cells more slowly returned to normal. Bantz² has stated there is a disturbance in balance between the

demand and production of blood cells so that the progress of infection is not combated. With such a lack of resistance to infection, it is not remarkable that necrotic lesions should find distribution in locations which harbor infective organisms. These lesions thus arise secondary to the blood changes.

The inflammatory sites wherever found have a similarity of appearance. The lack of cellular response must be the result of the general decrease of cells in the circulating blood. Rotter,²¹ however, noted that the number of cells in the microscopic sections of 10 of the cases were disproportionate to the number of cells in the blood.

The microscopic appearance of the pneumonia which is a frequent cause of death has not been described. The extensive fibrinous and hemorrhagic exudate as in other lesions was almost acellular. It is not known whether the absence of leukocytes is a factor in the massive production of fibrin or whether the particular etiologic agent is the stimulus.

The etiologic agent has thus far not been determined and it is difficult to attach much significance to the varied bacteriologic findings. No mention has previously been made of a spirochete of the bifidus type as was found in Case II. The work of Lovett¹³ with *Bacillus pyocyaneus* is the only successful animal experimental work on etiology. By using bacterial suspensions intraperitoneally Lovett¹³ produced a blood picture in guinea pigs similar to that found in the patient from whom the organism was isolated. We are impressed with the fact that there is no epidemic character to the disease.

There has been no indication that status thymolympathicus plays a part. Only 1 case has shown anatomic anomalies at autopsy (Feer⁷). There is also no apparent congenital disposition to agranulocytic blood changes. In the cases of recovery, the blood picture has returned entirely to normal. The case of Ehrmann and Preuss⁵ during convalescence had a second febrile attack which produced no blood or tissue changes. The case of Moore and Wieder,¹⁷ however, succumbed to a second attack after an interval of good health. It would appear that the factors which bring about the clinical state must depend on an inconstant individual resistance to the etiologic agent.

Differential Diagnosis. In the differential diagnosis of angulocytic angina, conditions must be considered which may produce similar anatomic or blood changes, as (1) Acute poisoning; (2) acute leukemia; (3) aleukemic leukemia; (4) sepsis.

1. Poisons such as thorium, arsenic, benzol and the Roentgen rays may produce leukopenia. Benzol attacks primarily the granulocytic cells. The Roentgen rays attack these cells secondary to the lymphocytes but may produce an associated gangrenous stomatitis (Leon¹¹). Our case No. 1, who had received arsenic in syphilitic

treatment, at autopsy showed no anatomic evidence of poisoning or of syphilis. Poisons may be ruled out by careful history of the case.

2. Acute leukemia in its fulminant form has an onset with high fever, mucous membrane and petechial hemorrhages, enlarged lymph nodes and spleen, stomatitis and leukocytosis above 50,000 cells. Bleeding from the mucous membranes and petechial hemorrhages are constant and usually precede gangrene. Abnormal lymphocytes are always seen in the blood smear. At autopsy, cellular infiltration is widespread and always present. Many variations of this picture have been described. Minot and Lee¹⁶ state that the enlargement of lymph nodes and spleen may be slight or the glandular enlargement may be confined to the cervical region. In agranulocytic angina, gross bleeding is seldom seen and clinical hemorrhagic diathesis has occurred only in less than one-fifth of the cases. Jaundice is seen in one-half. Few cases have shown weak attempts at lymphoid infiltration and abnormal cell formation, but in Zadek's²⁸ opinion such findings are not unusual in severe infections. None have shown frank evidence of leukemia at autopsy.

3. Aleukemic leukemia usually regarded as a type or initial phase of leukemia shows the clinical characteristics of ordinary leukemia, as noted above. The blood cell count is low or below normal. There is relative lymphocytosis with immature and abnormal lymphoid forms and decrease of granular cells. As these cases progress the blood picture usually tends to assume the leukemic form especially with regard to the differential count. Should the case come to autopsy in the leukopenic stage lymphoid infiltrations of organs are almost always found. The present opinion is that agranulocytic angina is a reaction which is not of the leukemic type. In some instances a positive differentiation must rest on the anatomic findings at autopsy.

4. Cases of sepsis were first described by Turk,²⁷ Marchand,¹⁴ and Stursberg²⁶ which showed neutrophilic leukopenia and relative lymphocytosis. These cases had gangrenous stomatitis, hemorrhagic diathesis, anemia and thrombopenia. Jaundice was uncommon. All had positive blood cultures and foci of sepsis at autopsy. Clinically the course of disease is similar to agranulocytic angina. However, only a small percentage of the latter cases have shown evidences of sepsis with positive blood cultures. At autopsy also the septic type of splenitis is not found. Some writers believe that the proven septic cases should be excluded from the group of agranulocytic angina. It would appear that both groups show a similar blood cell response to infection.

The inflammatory sites in agranulocytic angina have a wide distribution, and in general would appear to be due to secondary infection. Few cases have had infectious lesions before the time of acute disease. It is entirely possible that some severe cases

should develop generalized infections in conjunction with the local inflammatory manifestations. Such an occurrence cannot give rise to a separate classification. Because of the similarity of response to infection writers have suggested an inclusive nomenclature. David⁴ mentions, "sepsis with granulocytic decrease," and Feer,⁷ "sepsis agranulocytica."

All cases which have been reported as agranulocytic angina do not show the clear-cut record of the original description. Variations in clinical manifestations must be expected as our experience in a particular group of symptoms widens. Case V of Zadek,²⁸ a male, aged twenty years, with leukocytosis is one which must be questioned. At no time had he leukopenia, the neutrophils decreased only to 22 per cent, recovery taking place in four weeks. The course in this instance simulates that described by Schultz,²² Sprunt and Evans,²⁵ Longcope¹² and Baader¹ as monocytic angina or infectious mononucleosis. The other cases of recovery show all of the clinical characteristics of agranulocytic angina.

Abnormal reactions of the hematopoietic system have been observed in many infectious diseases. The diagnosis of agranulocytic angina and the allied diseases rests on the composite clinical picture and not the various symptoms. Turk²⁷ has stated, "the leukocyte picture of blood in infection is the result of the type and strength of infection on the one hand and the individual with spontaneous power of reaction of the diseased tissue on the other." In dealing with a biologic reaction of unknown etiology it will be necessary to collect and correlate many cases with autopsy confirmation to establish the reaction as a clinical entity.

Summary. Two cases of agranulocytic angina are reported and 43 cases are reviewed. Agranulocytic angina occurs at all ages in both sexes but more commonly in females. It is manifested by sudden rise of fever, sore throat, dysphagia, chills and malaise, which progress to severe toxemia and prostration. The onset usually comes in a period of good health, but may follow various chronic conditions. The symptomatology is not constant. Stomatitis is always present. There may be regional adenopathy and enlargement of the liver and spleen. Jaundice is common, while petechial hemorrhages are rare. The blood change of neutrophilic leukopenia with relative lymphocytosis is always seen. These blood changes are the result of the primary action of an unknown etiologic agent on the bone marrow. A slight secondary anemia is sometimes seen. The ulcerative sites in the mouth and at various locations arise secondary to the blood changes, due to decrease in the body resistance to infection. The ulcerative sites show a lack of the cellular response of inflammation. This same lack of cellular response is seen in the pneumonic process which usually leads to death. The disease does not always terminate fatally. On recovery, the blood picture returns to normal. The recovered cases may have a second attack of the disease.

Differential diagnosis in agranulocytic angina presents points similar to the reaction to specific poisons, lymphocytic leukemia, alymphatic leukemia and cases of sepsis with leukopenia. It does not fall within the classification of these conditions but with the evidence at hand it cannot be called a clinical entity.

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THE TREATMENT OF CHRONIC CONSTIPATION.

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THERE are probably more drugs in use for the treatment of constipation than for any other human ill. Salines and mineral waters, herbs, teas—their name is legion. Besides drugs, enemata, irrigations, exercises, massages, vibrations and electricity have all been vaunted by their enthusiasts as the treatment *par excellence*.

There are many gradations in this disease—from the mildest costiveness to almost complete obstruction. Some constipated patients will obtain a daily movement of their bowels by eating an apple or some stewed prunes or drinking a glass of hot or cold water on arising. Others will be benefited by a little olive oil or mineral oil, by cold milk or buttermilk. In many cases a change in diet, the addition of fruits, vegetables or bran, or, in others, a little exercise will bring about the desired result. In some patients constipation is due merely to laziness and is easily corrected by setting aside a few minutes after breakfast for the important function of moving the bowels.

When a patient presents himself for treatment of constipation the physician should take a careful history, inquire into the habits of the patient with regard to diet, water drinking, smoking, exercise, use and abuse of laxatives and enemata. A thorough physical examination should include not only the mouth, teeth, chest and abdomen, but also the anus, rectum and sigmoid. If the result of the examination is negative the patient is put on a diet of fruit, vegetables, bran, whole-wheat bread and fatty foods (unless he be obese). He is advised to drink much water and to make an attempt to move his bowels at a definite time each day, preferably after breakfast. A moderate amount of exercise is prescribed. He is given two or three tablespoonsful of mineral oil daily.

If a daily movement of the bowels does not result from following these instructions the patient is advised to inject from 4 to 8 ounces of warm Mazola oil into his rectum before retiring. This should be carried out with the patient lying on his left side with the hips higher than his shoulders. The oil is injected slowly, and is retained until the following morning. If 8 ounces cannot be retained comfortably 6 ounces or less should be used. Most patients can well tolerate 8 ounces.

The following morning after breakfast the patient should attempt to move his bowels. If unsuccessful he should inject a small quantity of warm water, not more than a pint. After the third or fourth day the water injection is usually unnecessary, as the patient will have a good movement without it.

After a week of daily oil injections these are given on alternate nights, then every third night, gradually decreasing the frequency until the patient has established the habit of a daily stool.

In some patients, however, the oil enema, even when followed by the injection of water, returns clear and no stool follows; in others there is a stool if the oil enema is used, but constipation recurs promptly when the oil enemata are stopped, even though all the directions concerning diet, exercise and the rest, detailed above, are rigidly followed. It is for such cases that the treatment to be described is proposed.

A complete gastrointestinal Roentgen ray examination is necessary to rule out definite obstruction such as tumors, kinks, bands, etc.; these, of course, require surgical treatment. A large number, however, will not show any such lesions, and the only finding will be a spasm of the descending colon, sigmoid, rectum and anus. This group will include the greater number of cases of constipation that do not respond to the dietetic and other treatment outlined above.

Two types of constipation are usually recognized: The atonic and the spastic. Of late, it has been found that the first type is very infrequent. The atony is usually due to a spasticity lower down in the colon. Mueller, of Vienna, says there is no atonic constipation.

In the spastic type of constipation the patient's reaction to an ordinary enema is often quite characteristic. Either the water will not flow in at all, or, if it does, will cause severe cramps because, being unable to pass into the sigmoid, it distends the rectum to the point of pain. If it does pass beyond the constricted point under the pressure of the water used for the enema, it remains in the higher colon, because there is not enough *vis a tergo* in the colon to expel it past the spastic portion of the sigmoid. This accounts for the patient's complaint, that enemata are not only painful but useless, as the water injected either fails to return or else returns clear.¹

Gant² found that by dilating the anus and rectum with Wales bougies he was able to cure a large percentage of his cases. The objection to this treatment is that in most cases the bougie cannot be introduced more than a few inches, as the introduction is by the sense of touch and it is impossible to pass it beyond the curves and bends of the sigmoid. When so much difficulty is often found in introducing an electrically lighted sigmoidoscope, where direct vision aids the sense of touch, one can realize the impossibility, in most cases, of blindly pushing a bougie to the desired distance.

Hirschman³ inserts into the rectum a rubber bag of the type of the obstetrical bag which is inflated and deflated a number of times, thus stretching the sphincters and rectum.

Both these methods are open to the objection that only the rectum or perhaps a very small part of the sigmoid is stretched,

while usually the spasm embraces the sigmoid and descending colon. I have employed these methods of treatment in a large number of patients, but the results have not been satisfactory.

The method about to be described has given me the most excellent results in the type of cases under discussion, *i. e.*, patients with no organic obstruction and in whom the treatment by diet, mineral oil and oil injections has not proved efficacious.

The treatment consists of two parts. 1. Dilation of the lower 30 cm. of the colon. With the patient in the knee-chest position, an electric sigmoidoscope is introduced in the usual way to its full length, and the patient allowed to recline for fifteen to twenty minutes, with the foot of the table elevated and the instrument held in place by an assistant or by the patient himself, to prevent it from slipping out. The anus, rectum, sigmoid and part of the descending colon are thus kept on the stretch continuously for fifteen minutes, and the repetition of this procedure several times finally produces a relaxation and widening of the lower bowel which are more or less permanent.

2. At the end of fifteen or twenty minutes a rectal tube is inserted through the full length of the sigmoidoscope. The latter is then withdrawn while the rectal tube is held firmly in place and prevented from coming out with the instrument. The end of the rectal tube, therefore, remains high up, 30 cm. from the anus. Two ounces of a 25 per cent solution of magnesium sulphate are injected through the tube into the sigmoid and descending colon, the tube pinched and withdrawn. This solution causes a relaxation of the musculature of the bowel and enhances the dilating effect produced by the sigmoidoscope. By this method the solution reaches a point much higher in the colon than when introduced through a rectal tube inserted directly into the rectum (Soper⁴).

This treatment is given daily for three days, then, skipping a day, two more days in succession, then gradually diminishing the frequency of the treatments until only one treatment a week is given. This is continued for four to six weeks, and then a treatment is given every other week. After a time one treatment a month is given and that should be kept up for several months.

I have employed this treatment in over 100 cases, and it has proved effective in all but 2 or 3 patients; in these the sigmoidoscope could not be introduced further than a few inches on account of marked angulation and reduplication in the sigmoid. In all cases where the instrument could be introduced 20 cm. or more the results have been uniformly successful. A few illustrative cases may be cited:

CASE I.—Mrs. B. S., aged forty-three years, had severe constipation for two years; the bowels never moved without a laxative; she gets severe headache when constipated, which is relieved by an enema, but has great difficulty before enema is effectual. She cannot retain the water, as it

causes her great pain. Roentgen ray examination showed no lesions except a spastic colon.

Treatment. Patient was put on a diet containing much fruit, vegetables, bran and water; mineral oil given three times a day. She was instructed to take oil enema every night. After five days she reported that the oil enemata were without result. The oil returned clear, as did the soapsuds enema taken the following morning. Colonic dilatation, by means of a sigmoidoscope, with the injection of magnesium sulphate, as described above, was instituted. After two treatments the oil enemata were quite effective. The treatment was continued for one month, during which time the frequency of both the dilatations and the oil enemata was gradually reduced. Three months after starting treatment the patient had regular and normal bowel movements with the aid of nothing more than a little mineral oil, taken once a day.

CASE II.—Mr. A. G., aged twenty-five years, has been constipated ever since he can remember. Treatment by diet, petrolatum and oil enemata was effective for a short time and then symptoms returned. Roentgen ray examination showed no lesions except a spastic colon. Treatment by sigmoidoscope with injections of magnesium sulphate for about two months brought about complete cure. The patient was seen two years afterward and said that his bowels moved daily without any laxatives or enemata.

CASE III.—Miss E. B., aged twenty-six years, has been troubled with obstinate constipation for many years; she has been treated by many physicians, by diet, medication and oil injections. The last were absolutely ineffectual and laxatives caused her extreme discomfort and pains. Roentgen examination was negative except for a spastic colon. She was put on sigmoidoscopic treatment and oil enemata were continued. Soon the injections began to produce good results, but she has had to continue taking oil injections about twice weekly, otherwise her bowels do not move. After every few weeks the oil injections begin to lose their effect, and she has to get one or two sigmoidoscopic treatments, after which her bowels move well again for several weeks. She has to come back for treatments less and less frequently as time goes on. She was one of the most obstinate cases of my series and, though she responded more slowly, her condition is much better now than it has been for years. She has no pain or cramps and has gained about 10 pounds in weight during the last few months.

Conclusion. A method is advocated for the treatment of chronic spastic constipation by dilatation of the lower intestinal tract with a sigmoidoscope and rectal tube.

In more than 100 cases it has proved successful in all but 2 or 3, where it was impossible to introduce the sigmoidoscope the necessary distance.

This treatment is advocated only in cases where treatment by diet, by mineral oil and by oil injections has proven ineffective. A Roentgen ray examination must be made to exclude organic obstruction.

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INFLUENZA AND ITS PULMONARY COMPLICATIONS.

A STUDY OF THE INCIDENCE AND CHARACTER OF THE MARCH, 1926,
EPIDEMIC IN PROVIDENCE AND AT BROWN UNIVERSITY.

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THERE are few diseases with which the general practitioner deals which give him less satisfaction in his work than does influenza. Unless he belongs to that class of uncritical optimists, a group all too large even in the ranks of regular medicine, and can see in the quick termination of each sharp attack, the brilliant success of his favorite method of treatment, he will find little in dealing with the disease to give him the satisfaction that comes from the accurate evaluation of signs, symptoms and laboratory data leading to a correct diagnosis and the prompt application of efficient therapy. The diagnosis of influenza is at best very indefinite. Even during the course of an epidemic there is variation in the clinical picture. When no epidemic prevails, many of the sporadic cases, usually termed "grippe," are quite indistinguishable from some forms of the "common cold" or from cases of tonsillitis or pharyngo-tracheitis, presumably of other origin. In the absence of any accurate pathognomonic signs or laboratory tests, the diagnosis must represent merely a clinical guess. For this reason the collection by the health authorities of accurate data as to the prevalence of the disease is impossible. The only available method of obtaining information as to its occurrence in a given community at a given time, is by a survey of the records of the practitioners of the community and a study of the institutions located in the community. Hospital statistics are usually of little value, as comparatively few patients are admitted to civil hospitals because of uncomplicated influenza.

It is the purpose of this communication to attempt to present some information regarding the March 1926 outbreak of influenza and its pulmonary complications as it occurred in Providence. It is based on a study of the incidence and character of the disease as it affected the student body of Brown University, and as observed by the writer in private practice in the community; and also on reports from their private records of ten representative physicians in the City of Providence and its environs.

The importance of the study of influenza does not need to be stressed to the people of this generation while we are still in the shadow of the pandemic of 1918. "The last of the great plagues" as Christian calls it, still scoffs at the efforts of man to check its

progress. But entirely apart from its terrible consequences when it becomes pandemic, the harm which influenza does in ordinary years and the occasional lesser and limited epidemics make its conquest one of the most pressing medical problems of the day. It is not only the mortality and morbidity from pneumonia and other complications of the disease which make it important, but the great loss of time and efficiency caused by simple uncomplicated cases. For example: at Brown University during the academic year 1924-1925, out of a student population of approximately 1200 men, 149 cases of influenza or "grippe" occurred and involved a total of four hundred and eighty-six days absence from class work. It was the cause of more loss of time than was any other illness, those most closely approximating it in this respect being "common colds," contagious jaundice and acute bronchitis. In the year 1925-1926, because of the March epidemic, the figures are much more striking. The cases of influenza totaled 359, of which 284 occurred in March, and caused a total absence from class work of one thousand six hundred and forty-four days. A comparison of the days of academic work lost because of the more important diseases during the two years under discussion is shown in Table I.

TABLE I.—ACADEMIC DAYS LOST BY STUDENTS AT BROWN UNIVERSITY BECAUSE OF THE MORE IMPORTANT DISEASES.

	1924-1925.	1925-1926.
Influenza	486	1644
"Common colds"	359	240
Contagious jaundice	254	99
Tonsillitis	205	188
Appendicitis	186	230
Gastrointestinal attacks	153	156
Pneumonia	151	46
Injuries	116	238

Since the pandemic of 1918 there have been repeated outbreaks of influenza in all parts of the world, as far as can be determined by the published reports, which, as has already been stated, must be meager and inaccurate because of the impossibility of collecting any figures as to the total incidence of the disease at any time in any community. Rhode Island practitioners will recall the early months of the year 1920 as a time when this state was especially afflicted. Every year the disease has recurred with greater or less severity and sporadic cases have been generally observed during every month of every year. It is the impression of the writer that the greatest incidence of the disease during the past seven years has been in March or late February and that a lesser "peak" has usually been observed in December. In the winter of 1924-1925, although no true epidemic could be said to exist, a great increase in the occurrence and severity of the disease in Rhode Island was noted in March. In the private practice of the writer, the number of influenza cases seen in March

was more than double those seen in any preceding month, and the same was true of cases seen in the student body at Brown University, and among the nursing staff and employees of the Rhode Island Hospital.

According to reports received by the State Board of Health, influenza, during the winter just past, can be said to have again become pandemic although in a form much less virulent than that seen in 1918. In Rhode Island the epidemic may be said to have begun in the first week of March and to have reached its peak in the third week. Table II shows the occurrence of the disease in the practice of ten active Providence practitioners, who, during the months of January, February, March and April, observed a total of 1170 cases. The occurrence of the disease among the student body of Brown University during the same period is also given in Table II.

TABLE II.

A. INCIDENCE OF INFLUENZA IN FIRST FOUR MONTHS OF 1926.

	January.	February.	March.	April.
Ten practitioners	115	169	674	212
Students at Brown	16	22	284	9

B. OCCURRENCE BY WEEKS (MARCH 1 TO APRIL 15).

	March.				April.	
	1 to 7.	8 to 14.	15 to 21.	21 to 31.	1 to 7.	8 to 14.
Ten practitioners	105	200	205	167	86	64
Students at Brown	30	90	107	57	3	0

This table shows that the "peak" was reached in the third week in March, both in the college and in the community. It suggests that the students represented particularly fertile "soil" for the infection. The relatively extreme incidence of the disease among the students at the height of the epidemic and the sudden dying out of the infection suggests that practically the whole student body was exposed during March, and that virtually all susceptible individuals were affected. It is interesting to note that of all the cases among students, there is no record of the occurrence of pneumonia, and two students only developed pulmonary signs which, in both cases, consisted merely of a few râles localized at one base and associated with the persistence of a slight fever for three or four days.

It is perhaps of some value for the writer to record his personal impressions of the epidemic, which in general correspond closely with those of other practitioners questioned on the subject. The main symptoms noted in the usual descriptions of the clinical aspect of the disease were present. Of these, headache, so intense at times as almost to suggest meningitis, was, in most of the severer cases, the most distressing symptom. General aches and pains

were marked in many cases. Cough and substernal discomfort was sometimes present and at other times absent. Even in the very severe cases, if cough was absent on the first day of fever, pulmonary complications almost never occurred, although one or two exceptions to this rule were noted. Coryza was not frequent. Sore throat occurred in many cases but usually was not severe. On examination a fairly mottled redness of pillars and pharynx spreading up over the soft palate was very frequently seen. Often, broad red bands running down the sides of the pharynx just behind the posterior pillars, "lateral pharyngitis," were observed. In general the appearance of the throat usually suggested a much greater degree of "soreness" than was felt by the patient. In a few instances the tonsils bore a follicular exudate without causing the patient to complain. In some cases no abnormality of the pharyngeal mucosa whatever could be seen. The temperature varied greatly but usually reached its maximum within twenty-four hours of the onset. The pulse in most cases was relatively low. The subjective symptoms, especially the headache, general aches and prostration, usually reached their height during the first day of the disease, and although on the second day the temperature often rose as high or nearly as high, the patient usually felt much more comfortable. The return of the temperature to normal ordinarily occurred from the third to the fifth day but the prostration and weakness often persisted for several days longer. A study of the 90 cases treated at the University infirmary showed that the average temperature on the afternoon of the second day was but 0.2 degree lower than on the first day and reached 98.6 on the morning of the third day.

The clinical impressions of the writer agree in the main with the picture as described in the literature except that in the pandemic of 1889-1890 and in the years following, coryza appears to have been a much more prominent symptom than in the epidemic under discussion and in the 1918 pandemic. The incubation period appeared to be about forty-eight hours, as is usually stated, and this was observed in several families where the man of the house came down with the disease, followed two days later by the rest of the family. The whole clinical aspect of the disease corresponded closely with that which has been generally observed since the pandemic of 1918. While old people and children were generally affected, it seemed that the greatest virulence was shown in young and middle aged adults. A few people were infected who had previously suffered from influenza within six months; which was to have been expected as the writer, in common no doubt with many other practitioners, has noted during the past seven years many instances of second and a few of third attacks of the disease in the same individual during a given winter and spring. Medication, as usual, appeared to have no effect in shortening the disease,

and the writer has received the impression that the free use of such antipyretic drugs as acetyl salicylic acid and phenacetin definitely tend to prolong the course of the fever by causing an artificial defervescence before bodily resistance to the infection has been established. Codein, barbital and occasionally morphin have been found useful in controlling the symptoms.

Of the complications, secondary invasion of the lungs was the only one which appeared to be of particular importance. The description written by Dr. F. T. Lord in "Osler's Modern Medicine" (1916) and based especially on the observation of sporadic cases, minor outbreaks and a severe localized epidemic in Boston in 1907-1908, is more suggestive of the pulmonary complications seen during the recent epidemic than are those accounts based on the pneumonias of the 1918 pandemic, when the virulence of the infection was at its height. Lord noted the frequent apical involvement, often resembling tuberculosis, the atypical nature of the pulmonary signs and the tendency to delayed resolution. In the recent epidemic all these same things have been prominent. Indeed it may be said of the pulmonary lesions, as judged by physical and Roentgen ray examination, that they are most varied, atypical and often bizarre. It is true, as will be seen in Table IV, that the incidence of frank lobar pneumonia was greatly increased during March. Small areas of invasion located anywhere in the lungs were also common. On examination many of these were indicated merely by a few fine râles without dullness, and in such cases the Roentgen ray often revealed definite, and at times, extensive areas of density. A few cases in which no physical signs whatever could be found showed well-marked lesions in the roentgenograms. On the other hand, in two instances noted, the reverse was true, that is to say, in the presence of the physical signs of consolidation, localized dullness, bronchial breathing and fine crepitant râles, the Roentgen ray plates (in one case, repeated many times) were absolutely negative.

Table IV indicates that the increase in pneumonia in March was principally due to the occurrence of cases which ran a somewhat atypical course, ending by lysis rather than crisis. Of the 41 pneumonias occurring at the Rhode Island Hospital in March, 29 were clearly lobar in distribution, 8 were doubtful and 3 were bronchopneumonia. Contrary to Lord's experience, empyema was rare. Delayed resolution was more common than empyema, and a few instances of this condition were observed in which the signs of consolidation persisted for several weeks but eventually totally disappeared. In 1 case of rather doubtful origin, in that the pneumonia appeared as a complication of a streptococcus septicemia following mastoiditis, the consolidation persisted four months, but had cleared completely at the end of five months. This case is not included in the statistics.

TABLE III.—ANALYSIS OF PNEUMONIA CASES IN INFLUENZA EPIDEMIC.

CASES FROM THE RECORDS OF TEN PRACTITIONERS AND THE RHODE ISLAND HOSPITAL.

	January.	February.	March.	April.	Grand total.
Ten practitioners	12	11	26	12	
Rhode Island Hospital . .	14	7	41	15	
Total	26	18	67	27	138

ENDING BY CRISIS.

Ten practitioners	6	7	4	3	
Rhode Island Hospital . .	3	1	7	2	
Totals	9	8	11	5	33

ENDING BY LYSIS.

Ten practitioners	4	2	17	4	
Rhode Island Hospital . .	2	0	11	6	
Totals	6	2	28	10	46

EMPHYEMA.

Ten practitioners	3	2	1	0	
Rhode Island Hospital . .	1	0	2	0	
Totals	4	2	3	0	9

DELAYED RESOLUTION.

Ten practitioners	2	0	3	1	
Rhode Island Hospital . .	0	0	2	2	
Totals	2	0	5	3	10

NOTE.—Cases of pneumonia complicating other diseases, excepting influenza, were excluded from consideration.

Many of the patients with frank lobar pneumonia gave a history of an influenzal attack immediately preceding the onset of the pneumonia, and three were under observation and received adequate bedrest and care during the whole course of their illness from the onset of the influenza to the recovery from the pneumonia.

The resemblance of some of the apical lesions to tuberculosis was very striking. One patient, a nurse, passed through a severe influenza and, with a continuation of the fever, developed a few râles at the right base. Roentgenograms revealed a slight haziness at both the right base and the left apex. During the next three weeks the signs at the base disappeared and definite dullness and fine râles appeared at the apex. The temperature rose every afternoon to 100.5° to 101° and the patient coughed up a moderate amount of sputum. Roentgen ray examination showed an increase in the apical lesion. During the next two weeks the condition persisted and the patient suffered repeated night sweats and a small hemoptysis consisting of about one teaspoonful of clear blood. A roentgenogram at this time revealed a rather extensive clouding

of the left apex and physical examination showed distinct dullness and fine crepitant râles in the same region, extending as low as the spine of the scapula. Then, rather abruptly, the afternoon elevation of temperature failed to occur. The cough lessened, the general condition improved, and two weeks later, after seven weeks, illness altogether, the patient left the hospital without symptoms or physical signs. A roentgenogram taken just before discharge showed only a very little clouding at the apex. Seen one month later, she appeared perfectly well and had remained so at the end of seven months after the onset.

Summary and Conclusions. A study of the incidence and character of the March 1926 epidemic in Providence and among the students of Brown University shows the following:

1. The disease was typical, and, though markedly contagious, was much less virulent than in 1918.

2. The epidemic reached its "peak" during the third week in March.

3. The students at Brown University were apparently very susceptible to infection, but resistant to secondary pulmonary involvement. While the incidence of the disease at Brown University was high, frank pneumonia did not occur and only two instances of very mild localized pulmonary invasion were observed.

4. Pulmonary complications among the citizens of Providence consisted of all gradations from frank lobar pneumonia to very slight mild localized areas of invasion, and included many atypical and bizarre forms, some in which resolution was markedly delayed, and some which involved the apices and strongly resembled tuberculosis. Many of the pneumonias that were lobar in distribution were atypical in course and ended by lysis.

NOTE.—My thanks are due to Prof. J. W. Wilson, of the Department of Biology, for his kindness in furnishing me with data collected by a questionnaire, which he sent to one hundred Providence practitioners.

THE POLYMORPHONUCLEAR LEUKOCYTE IN THE TUBERCULOUS BLOOD PICTURE.

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THE typical blood picture of tuberculous individuals is considered to be a low white count with a relative increase of lymphocytes and

a relative decrease of polymorphonuclear leukocytes. When a leukocytosis with a relative increase of polymorphonuclear leukocytes occurs in tuberculous cases it is generally believed to be the result of secondary infection. Since the report¹ of one of us with regard to the important part played by the polymorphonuclear leukocyte in the process of caseation, it appeared to be of interest to study the blood counts in tuberculous cases to ascertain whether there might be evidence of clinical value to be obtained from the increase or decrease of this cell in the circulating blood.

The report submitted below is a brief résumé of the cases that have been observed in the Wisconsin General Hospital for the past two years. At the time these records were made, no especial attention to the blood picture as it concerned tuberculosis was given. Consequently, there are numerous omissions which it would be highly desirable to fill in if it were possible. Blood counts were done at very irregular intervals and often only when sepsis was considered. In numerous instances differential counts were not done. Several cases that came to autopsy had not had blood counts done for weeks prior to death. In other instances, the cases were observed but a few days and only one blood count was done. In spite of these unavoidable lapses in the blood counts, they are of great value because they represent a cross section of the blood picture in tuberculosis from an unbiased viewpoint.

Sixty-seven cases without death and 6 cases which came to autopsy comprise this study. The 67 cases represent all clinical stages of tuberculosis and included medical, orthopedic and surgical cases. The age range was from two to seventy-one years.

No attempt will be made here to analyze these cases except an occasional one which showed a blood picture of significance. An analysis of the blood counts in these cases gives the following facts. 247 blood counts and 119 differential counts were made. Twenty-four cases had but one count. Twenty-six cases had three or more counts. The remainder had two counts.

Fifty-six of these cases showed the leukocytes above 9000 in some counts. The counts ranged from 9200 to 38,000. Fourteen cases showed 7500 or less in some counts. The range was from 7500 to 4800.

Forty cases had over 70 per cent of polymorphonuclear leukocytes in some counts. The range was 71 to 95 per cent. Eight cases had less than 60 per cent, the range being 59 to 40 per cent. Seventeen cases showed between 60 and 70 per cent in some counts.

Twenty-nine cases had over 25 per cent of lymphocytes, the range being 26 to 64 per cent. Thirty cases had less than 20 per cent, the range being 19 to 5 per cent. Eight cases had 20 to 25 per cent.

The eosinophils ranged from 0 to 5 per cent and the mononuclear leukocytes from 0 to 11 per cent.

Case Abstracts. The following cases are briefly given as they had blood counts of especial interest:

No. 384. Female, aged thirteen years. One year ago she was severely ill and was in bed several weeks and a diagnosis of typhoid fever was made. Fever has been present for the year, night sweats have been numerous, there has been some cough, but little expectoration. She has had pain in her chest and pleurisy was diagnosed. At times fiery-red spots have developed on her ankles, wrists, forearms, legs, and so forth. The child presented the picture of an extreme septic condition. Temperature 99° to 105° . Blood cultures were negative. Chest examination showed areas of dullness, râles and bronchovesicular breathing. Examination of the sputum was positive for tubercle bacilli. The child was in the hospital two months and showed some clinical improvement following sun baths. She was discharged to a tuberculosis sanatorium.

Leukocyte counts done were as follows:

Total count of 37,800 leukocytes, the differential count being neutrophils 81 per cent (30,618 neutrophils); lymphocytes, 16 per cent (5948); large mononuclear, 2 per cent; transitionals, 1 per cent; 18 more total counts varied between 13,000 and 25,600, the last being 22,000 at time of discharge.

This case would have been far more instructive had differential counts been done. The only differential showed an apparent increase in polymorphonuclear leukocytes and an apparent decrease in lymphocytes. Actually there were 30,618 polymorphonuclear leukocytes and 5948 lymphocytes per cubic millimeter. The case shows that a high leukocytosis can occur in an active case of pulmonary tuberculosis without substantiated evidence of secondary infection and that the differential count can simulate that of a pyogenic infection.

No. 254. Male, aged nineteen years, had been a rather sickly youngster until fourteen years of age. Onset of the present illness was six months ago: he felt tired, had several colds, and occasional night sweats. He has lost 15 pounds and complains of pain in the left chest on inspiration. Physical examination showed a moderately advanced bilateral pulmonary tuberculosis, and the sputum was positive for tubercle bacilli. During his stay in the hospital the patient developed an acute abdominal condition which proved to be a tuberculous peritonitis. The temperature ranged from 97° to 102° . He was in the hospital two months and showed some clinical improvement, and was finally taken home by his parents for continuance of treatment.

The leukocyte counts done were as follows:

Differential count.							
Total count.	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	Eosinophils.	Transitionals.
8,220	80%	6,576	17%	1,397	..	1%	2%
8,000	75%	6,000	22%	1,760	3%
7,400	56%	4,140	32%	2,368	6%	4%	1%
9,950	75%	7,425	21%	2,089	4%
9,750	75%	7,312	20%	1,950	4%	1%	..
12,000	74%	8,800	23%	2,760	1%	1%	..
9,750	75%	7,312	11%	1,072	4%	3%	7%

This case is instructive in that the differential counts showed an actual increase in the polymorphonuclear leukocytes in all but the third count in spite of the fact that the total leukocyte count was never very high. The third count showed what is generally accepted as a typical blood picture of tuberculosis. Between the third and fourth count the case developed tuberculous peritonitis. There evidently was a spread of the tuberculous process and the blood picture was that of a mild septic process.

No. 2965. Male, aged nineteen years. The patient has been under treatment at a sanatorium for over a year and was sent in for surgical treatment of a fistula in ano. He showed far-advanced bilateral pulmonary

tuberculosis with cavitation and tuberculous enteritis, and he was discharged to the sanatorium unrelieved.

The leukocyte counts done were as follows:

Differential count.						
Total count.	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclear.	Eosinophils. Transitional.
22,200	75%	16,650	17%	3,774	2%	6%
23,000						
14,700	80%	11,760	14%	2,058	4%	2%

Nine other counts varied between 14,600 and 28,600.

The blood picture in this case would usually be ascribed to secondary infection. It could more logically be ascribed to the active, spreading, caseating tuberculous lesions. The patient has not improved under sanatorium treatment and is growing progressively worse.

No. 832. Female, aged twelve years. The patient was sent into the hospital because of hip disease of two years' duration. Four years ago the patient had "rheumatism" in the same leg. The hip was painful. Roentgen ray and clinical diagnosis was tuberculosis of hip. A brace was applied and patient was discharged to return in four months.

The leukocyte counts done were as follows:

Differential count.						
Total count.	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclear.	Eosinophils.
6,400	58%	3,712	32%	2,048	8%	2%
13,200	72%	9,504	24%	3,168	3%	1%

Four months later the patient returned. There was good progress clinically: she was gaining in weight and strength, and the hip was much better.

The leukocyte count was as follows:

Differential count.						
Total count.	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclear.	Eosinophils.
7,200	40%	2,880	40%	2,880	8%	

No. 2021. Female, aged eight years. Patient had pneumonia when two, three and four years of age. She had pain in the back with deformity over a year. Examination showed a tuberculous process involving the 11th and 12th thoracic and first and second lumbar vertebrae. An Albee operation was performed and a brace applied. No abscess was found at operation. The patient made excellent clinical progress.

The leukocyte counts done were as follows:

Differential count.						
Total count.	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclear.	Eosinophils.
7,400	42%	3,180	44%	3,256	12%	2%
6,000						
6,900	48%	3,312	37%	2,553	11%	3%
4,800	52%	2,496	44%	2,112	3%	1%

No. 147. Female, aged twenty-three years. Patient had influenza and pneumonia in 1918. Three years ago she began feeling poorly again and at that time was told she had pulmonary tuberculosis. For the past year she has had pain in the right chest, more severe in the past two weeks. Clinical examination and Roentgen ray showed bilateral apical tuberculosis. There was a fluctuating mass over the costochondral junction on the right side.

This was surgically drained and proved to be tuberculous. She was discharged after drainage, to report for surgical dressings.

The leukocyte count done was as follows:

Total count.	Differential count.					
	Neutrophils.	Total.	Lymphocytes.	Total.	Eosinophils.	Transitionals.
9,600	88%	8,448	5%	480	1%	6%

The following are the records of the tuberculous cases which have come to autopsy. The cases are briefly summarized to give the essential facts, together with the blood picture as it was recorded. For sake of comparison the cases are arranged under three headings: Cases without cavitation of the lungs or draining sinuses; cases without cavitation of the lungs but with draining sinuses, and cases with cavitation of the lungs which did or did not have draining sinuses.

CASES WITH PULMONARY OR GENERALIZED MILIARY TUBERCULOSIS WITHOUT PULMONARY CAVITATION OR DRAINING SINUSES. No. 3770. Male, aged sixty-one years. Laborer. Typical tuberculous history. Hoarseness four weeks. Hospital one month. Clinical diagnosis: Advanced bilateral pulmonary tuberculosis. Tuberculous laryngitis. Sputum positive for tubercle bacilli.

Autopsy. Caseous bronchopneumonia without cavitation, bilateral; tuberculous ulceration of trachea and larynx; tuberculous ulceration of intestine; tuberculosis of spleen, both kidneys and liver; cholelithiasis; pleural adhesions, bilateral; emaciation.

The leukocyte counts done were as follows:

Differential count.

Total count.	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	Eosinophils.	Basophils.
8,700	79%	6,873	10%	870	7%	3%	1%
13,800	77%	10,626	11%	1,518	10%	1%	1%
11,800	85%	10,030	10%	1,180	..	1%	..

No. 4574. Female, aged sixteen years. Heartburn for years; tachycardia; dyspnea; flu, 1918; thyroid palpable; atrophic tongue; Melchlorhydria; blood culture negative; blood in stools; marked anemia; septic temperature, 100° to 104°. Hospital six weeks. Clinical diagnosis (provisional): pernicious anemia. Tuberculosis questioned.

Autopsy. Bilateral caseous bronchopneumonia without cavitation; extensive tuberculous ulceration of bowel with hemorrhage; tuberculosis of spleen and liver; old rheumatic endocarditis, mitral valve; obliterative pleuritis, bilateral.

The leukocyte counts done were as follows:

Differential count.

Total count.	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	Eosinophils.
7,500	80%	5,810	10%	1,387	1%	..
1,800	70%	1,260	28%	504	2%	..
2,150	68%	1,462	37%	795	5%	..
	56%	..	40%	..	4%	..
	61%	..	37%	..	2%	..
	75%	..	21%	..	4%	..
	80%	..	18%	..	2%	..
	86%	..	31%	..	3%	..
	86%	..	14%	..	1%	..
	85%	..	14%	..	5%	1%
	83%	..	11%	..	6%	2%
2,350	68%	1,594	26%	611	6%	..
	82%	..	14%	..	4%	..
	74%	..	20%	..	6%	..
	72%	..	21%	..	7%	..

The red blood cell picture was strongly suggestive of pernicious anemia.

No. 2368. Female, aged ten years. Headache and vomiting; delirious; vomiting ten days' duration. Kernig and Babinski positive. Spinal fluid positive for tubercle bacilli. Hospital one week. Clinical diagnosis: Tuberculous meningitis.

Autopsy. Generalized miliary tuberculosis. No cavities in lungs. Caseous peribronchial lymph nodes.

The leukocyte count was as follows:

Total count.	Differential count.				Mono-nuclears.
	Neutrophils.	Total.	Lymphocytes.	Total.	
14,400	82%	11,808	10%	1,440	8%

No. 5571. Female, aged twenty-two years. Dyspnea for four months, blurring of vision, edema of ankles, no cough, some diarrhea, ascites, hydrothorax. Râles at apex. Hospital two weeks. Clinical diagnosis. Nephritis. Tabes mesenterica. Myocarditis.

Autopsy. Tuberculous bronchopneumonia, no cavitation; generalized miliary tuberculosis; tuberculous peritonitis; fibrinous pleurisy; caseous peribronchial lymph nodes; anasarca; myocarditis.

The leukocyte count was as follows:

Total count.	Differential count.				Mono-nuclears.
	Neutrophils.	Total.	Lymphocytes.	Total.	
10,300	89%	9,167	8%	824	3%

No. 5580. Female, aged forty-seven years. Pain in abdomen for four months, palpitation, night sweats. Mitral presystolic murmur, abdomen distended, liver enlarged, ascites, pleural effusion. Hospital one week. Clinical diagnosis: Mitral stenosis with decompensation.

Autopsy. Generalized miliary tuberculosis; tuberculous peritonitis; congestion of lungs; fibrous myocarditis; pleural effusion; ascites.

The leukocyte count was as follows:

Total count.	Differential count.					Eosinophils.
	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	
12,250	83%	10,167	8%	980	4%	5%

No. 5448. Male, aged thirty-eight years. Weakness for eight weeks. Headache, fever, irrational, nausea and vomiting. Positive Kernig. Hospital one week. Clinical diagnosis: Cerebrospinal (lues). Tuberculous meningitis. (?)

Autopsy. Generalized miliary tuberculosis; tuberculosis meningitis; tuberculous mesenteric and retroperitoneal lymph nodes; old healed bilateral pulmonary tuberculosis; old pleural and abdominal adhesions.

The leukocyte counts were as follows:

Total count.	Differential count.				Mono-nuclears.
	Neutrophils.	Total.	Lymphocytes.	Total.	
7,550	94%	7,097	4%	302	2%
8,750	86%	7,525	8%	700	6%

No. 4830. Female, aged seventeen years. Headache, fever, Kernig positive. Hip trouble six months, night sweats during past few months. Backache. Mental changes recently. Tâche cerebrale. Absent reflexes. Babinski positive. Hospital six days. Clinical diagnosis: Tuberculous meningitis.(?)

Autopsy. Bilateral tuberculous bronchopneumonia without cavitation. Tuberculous meningitis. Generalized miliary tuberculosis. Bilateral obliterative pleuritis.

The leukocyte count was as follows:

Total count.	Differential count.				
	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.
11,000	81%	8,910	17%	1,870	2%

No. 2984. Male, aged forty-one years. Came to hospital because of a painful wrist which he had had for five years. During past two years he has lost 50 pounds in weight. He has been more or less incontinent for past seven years. There has been hematuria and marked frequency. Hospital two weeks. Clinical diagnosis: Tuberculosis of left wrist. Genito-urinary tuberculosis. Pulmonary emphysema.

Autopsy. Bilateral renal phthisis. Miliary tuberculosis of lungs, spleen and liver. Tuberculosis of left wrist. Tuberculosis of bladder and prostate. Emphysema and edema of lungs. Dilated right heart. Congestion of spleen and liver. Old obliterative pleuritis.

The leukocyte count was as follows:

Total count.	Differential count.				
	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.
11,700	76%	8,892	16%	1,872	8%

CASES WITH DRAINING SINUSES BUT WITHOUT PULMONARY CAVITATION.
No. 1815. Female, aged twenty-four years. Pain in back one and a half years ago. Draining sinus in right axillary region for three months. Acute pain in right flank three days, fever, headache. Fluctuant area in right back which was drained. Developed psoas abscess. Was in hospital six months with septic temperature. Clinical diagnosis: Pneumonia. Empyema. Psoas abscess.

Autopsy. Caries of thoracic vertebrae (tuberculous); psoas abscess (tuberculous from carious vertebrae); hypostatic bronchopneumonia (right lung); tuberculous spleen, liver, intestines, Fallopian tubes, uterus; tuberculous peritonitis, pelvic; old obliterative pleuritis right; tuberculous peribronchial lymph nodes, caseous.

The leukocyte counts done were as follows:

Total count.	Differential count.					
	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	Eosinophils.
13,200	77%	10,161	10%	1,320	10%	1%
12,200	79%	9,368	19%	2,218		
12,500	80%	10,000	16%	2,000		
11,500	80%	11,600	11%	1,595		
11,800	79%	9,322	16%	1,588		
12,300	75%	9,375	23%	2,875		
14,400	70%	11,276	11%	1,554		
14,100	85%	11,985	10%	1,410		
11,700	81%	11,907	16%	2,352		
9,500	72%	7,050	18%	1,764		
11,400	80%	9,120	16%	1,524		
14,000	86%	12,010	8%	1,120		
15,700	82%	12,874	13%	2,011		
18,200	81%	14,742	12%	2,184		
12,600	81%	10,208	13%	1,638		
20,600	78%	16,098	14%	2,884		
21,400	81%	17,331	17%	3,633		
16,600	83%	13,768	8%	1,228		
15,400	76%	11,704	18%	2,772		
16,000	88%	14,098	7%	1,162		
23,600	88%	20,768	7%	1,662		
13,400	85%	11,390	13%	1,742		
18,200	86%	16,198	9%	1,628		

Twenty more counts without differential ranged from 12,000 to 36,000.

No. 2840. Male, aged twenty-three years. Pulmonary tuberculosis four years with sanatorium treatment one year. Hemoptysis and other symptoms of tuberculosis present. Both testes removed for tuberculous epididymitis. Pain and swelling in back for two months. In hospital one month. Clinical diagnosis: Pulmonary tuberculosis. Renal tuberculosis. Subdiaphragmatic abscess, drained surgically. No open sinuses before this date.

Autopsy. Bilateral renal phthisis; perirenal abscess, tuberculous; tuberculous peritonitis; tuberculous cystitis and prostatitis; tuberculous enteritis; bilateral pulmonary tuberculosis without cavitation.

The leukocyte counts were as follows:

Total count.	Differential count.			
	Neutrophils.	Total.	Lymphocytes.	Total.
28,200	95%	26,790	2%	564
15,200				
25,700				
22,000				

CASES WITH PULMONARY CAVITATION AND WITH OR WITHOUT DRAINING SINUSES. No. 1230. Female, aged twenty-nine years. Discharging hip six months, pain in back eight months, two inguinal sinuses. Clinical evidence of apical tuberculosis. Roentgen-ray showed caries of lumbar vertebræ. Hospital eighteen days. Clinical diagnosis: Pulmonary tuberculosis. Pott's disease.

Autopsy. Tuberculous bronchopneumonia with small cavities present; generalized miliary tuberculosis; caries of lumbar vertebræ and sacrum, tuberculous; old rheumatic endocarditis; old obliterative pleuritis; ascites; fatty infiltration of liver.

The leukocyte count was as follows:

Total count.	Differential count.			
	Neutrophils.	Total.	Lymphocytes.	Total.
13,200	89%	11,748	10%	1,320

No. 5014. Male, aged fifty-two years. Patient from tuberculosis sanatorium sent in for treatment of ischio-rectal sinus. Diarrhea for nine months. Marked loss of weight and other symptoms of tuberculosis. Hospital four days. Clinical diagnosis: Advanced pulmonary tuberculosis with cavitation. Ischio-rectal abscess. Tuberculous laryngitis and enteritis. Renal tuberculosis.

Autopsy. Caseous pneumonia with cavitation. Tuberculous enteritis. Tuberculosis of spleen, liver, adrenals, kidneys and bladder. Fibrous myocarditis.

The leukocyte count was as follows:

Total count.	Differential count.					
	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	Transitional.
7,500	76%	5,700	20%	1,500	2%	2%

No. 1716. Male, aged fifty-one years. Symptoms one year with loss of weight, fever, productive cough, diarrhea one month. Hospital one month. Clinical diagnosis: Pulmonary tuberculosis with cavitation. Intestinal tuberculosis.

Autopsy. Bilateral pulmonary tuberculosis with extensive cavitation and caseous pneumonia. Tuberculous enteritis. Old mitral endocarditis. Chronic passive congestion of spleen and liver.

The leukocyte counts were as follows:

Total count.	Differential count.					
	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	Eosinophils.
16,200	85%	13,770	6%	972	8%	1%
15,300	80%	12,240	14%	1,842	5%	1%

No. 4494. Male, aged thirty-three years. Diagnosed pulmonary tuberculosis two years ago. Sanatorium treatment one year. Hospital one month. Clinical diagnosis: Far advanced pulmonary tuberculosis. Tuberculous enteritis.

Autopsy. Bilateral pulmonary tuberculosis with large cavities and areas of caseous pneumonia. Tuberculous enteritis. Miliary tuberculosis, generalized.

The leukocyte count was as follows:

Total count.	Differential count.					
	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	Eosinophils.
17,750	79%	14,022	15%	2,662	5%	1%

No. 4218. Female, aged twenty-four years. Pulmonary tuberculosis of four years' duration. Attacks of hysteria past three weeks. Hospital seven weeks. Clinical diagnosis: Bilateral pulmonary tuberculosis with cavitation. Intoxication psychosis with catatonic stupor.

Autopsy. Bilateral pulmonary tuberculosis with cavitation and areas of caseous pneumonia. Tuberculous enteritis. Renal tuberculosis. Tuberculosis of spleen. Subdiaphragmatic abscess, tuberculous.

The leukocyte counts were as follows.

Total count.	Differential count.					
	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	Eosinophils.
18,800	78%	14,664	15%	2,820	6%	1%
13,700						
33,500	86%	28,010	8%	2,050	6%	

No. 3059. Female, aged thirty-four years. Pain in back developed thirteen years ago. Local swelling. Developed paraplegia three months before admission to hospital. Hospital eleven months. Clinical diagnosis: Pott's disease. Advanced pulmonary tuberculosis.

Autopsy. Bilateral pulmonary tuberculosis with cavitation and areas of caseous pneumonia. Generalized miliary tuberculosis. Tuberculosis of cervical and thoracic spine. Psoas abscess. Tuberculous peritonitis.

The leukocyte counts were as follows:

Total count.	Differential count.					
	Neutrophils.	Total.	Lymphocytes.	Total.	Mono-nuclears.	Transitionals.
7,550						
6,800	73%	5,511	24%	1,812	2%	1%
9,600						
8,600						
9,000						

The last count was eight months before death.

Discussion. No attempt will be made to quote at length from the extensive literature on the blood picture in tuberculosis. The majority of writers are agreed that a low polymorphonuclear leuko-

cyte count accompanied by a high lymphocyte count is a good prognostic sign. The appearance of a high polymorphonuclear leukocyte count together with a diminished lymphocyte count is generally considered to be due to secondary infection with pus-producing bacteria. This idea rests largely upon the fact that bacteriologic examinations of pulmonary cavities very commonly demonstrate the presence of cocci of one type or another.

Kalkbrenner² gives an excellent summary of the views of various authors on the significance of the blood picture in tuberculosis. He followed the blood picture carefully over a long period of time in 185 cases of pulmonary tuberculosis. His conclusions are very significant. A short abstract of his article follows: "To gain a proper perspective the blood count must be followed from the beginning to the end of the disease. The initial reaction is a lymphocytosis which remains high in direct proportion to the resistance of the individual. At the height of the pathologic process there is an increase of the polymorphonuclear leukocytes which remains in the active chronic forms. Pathologically this change is seen with bronchopneumonia, caseous pneumonia, cavity formation, extension of the process to other organs and in complications, such as grippes, typhus, and so forth. The worse the case the greater the increase of neutrophils and decrease of lymphocytes. With clinical improvement this picture is reversed. If the lymphocytes do not fall too low there is a possibility of the patient overcoming the infection. There are no sharp lines of distinction to be drawn in the interpretation of the blood picture. On healing, the blood picture returns to normal. All patients should have the advantage of thorough blood examinations. These with the help of other factors are of use in determining the phase of the disease and the method of treatment."

Spooner³ found no evidence of secondary infection in ten tuberculous kidneys surgically removed. His opening paragraph is so pertinent that it is here quoted *verbatim*. "For years, a popular belief has existed that the septic manifestations of tuberculosis were due to a mixed infection with pyogenic organisms, that cavities containing caseous and purulent material resulted from the action of such organisms. Leukocytosis in connection with tuberculous infection was supposed to result from this mixed infection; though at the present time Sahli is beginning to see light, when he states that the degree of such a leukocytosis is due to the intensity of the tuberculous process, rather than to invasion by any other organism."

In a study of the process of caseation¹ recently reported by one of us the time of appearance and the significance of the neutrophil, the mononuclear leukocyte and the lymphocyte in the tuberculous lesion was emphasized. The typical tubercle without giant-cell formation or caseation is the first reaction to the tubercle bacillus. This is formed by the mononuclear leukocytes with practically no participation of the neutrophil or the lymphocyte. If the infection

is overcome with but little damage to the tissues, lymphocytes appear in the healing stage. If there is considerable necrosis of tissue in the individual lesion the neutrophils congregate in smaller or larger numbers. If the infection persists the neutrophils continue to accumulate and die. At this stage the typical picture of caseation appears. After caseation is produced the neutrophil is but little attracted. In the repair of this caseous area the lymphocytes and the mononuclear leukocytes congregate around and invade the area of dead inflammatory exudate.

It is fully recognized that the material submitted in this report is not the type from which definite conclusions may be drawn. It is felt, however, that it does show a cross section of the blood picture as seen in tuberculous cases from an entirely unbiased point of view. There are several things of significance that are deemed worthy of comment. Eighty-three per cent of the cases, exclusive of those autopsied, had a leukocytosis. Seventy-one per cent of these cases had a definite increase of polymorphonuclear leukocytes and 53 per cent had a definite decrease in lymphocytes.

Every case which was hospitalized for two weeks or more and which did not show good clinical progress had a leukocytosis with an increase of polymorphonuclear leukocytes. Those cases which showed good clinical progress all showed a normal to a high lymphocyte count. Some of these cases also had a leukocytosis.

In tuberculosis it appears that a differential blood count is of greater value than the total white count. It is necessary, however, to have both in order to determine whether there is an actual increase or decrease in the number of neutrophils or lymphocytes. In many of the cases here recorded a computation of the number of these cells shows an actual increase in both types, whereas on a percentage basis the lymphocytes appear fewer than normal. In any case of active tuberculosis one commonly finds lesions in various stages of formation, caseation and repair. Since the lymphocytes play a large rôle in the repair process, one should expect to find and does find an actual increase of their numbers in the circulating blood. On the other hand, a failure of the lymphoid apparatus to respond would suggest the inability of the individual to repair the damaged areas. It also appears essential to follow the blood count regularly during the course of the disease as there is often a great variation in the blood picture from week to week.

Every case that came to autopsy showed an increase in neutrophils regardless of whether there was present cavitation or draining sinuses. Some of these records go back for weeks and months before the death of the patient.

If an increase of polymorphonuclear leukocytes in tuberculous cases is an indication of secondary infection, then it appears that secondary infection is very common, regardless of cavitation or sinuses. We are not of the opinion that this represents secondary

infection, but rather that it represents an active, progressive, caseating tuberculous lesion. The degree of leukocytosis and of increase of neutrophils is an indication of the severity of the tuberculous infection.

At the present time the blood picture in several cases is being carefully followed over a longer period of time. This study will be reported at a later date.

Conclusions. The clinical blood picture in tuberculosis substantiates the important rôle played by the polymorphonuclear leukocyte in the process of caseation recently reported by one of us.

An impression is gained that an increase of neutrophils in tuberculosis is an indication of a progressive caseating lesion, hence a bad prognostic sign.

Total and differential white blood counts are of clinical significance in tuberculosis and should be more commonly and thoroughly done.

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SYSTOLIC HYPERTENSION.

ITS RELATIONSHIP TO ATHEROSCLEROSIS OF THE AORTA AND LARGER ARTERIES.

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SINCE hypertension or elevated blood pressure is merely a symptom, a better understanding of the condition must rest on an adequate nosologic classification. In the light of our present knowledge, cases of hypertension may be grouped into the following categories: (1) Hypertension associated with glomerular nephritis. (2) Essential hypertension, which is not associated with any known etiologic factor, and seems to be determined by a functional narrowing of the peripheral vascular bed; in its broad sense this is merely a makeshift inclusive class, in which are placed all cases of elevated blood pressure which are not associated with any known cause; as our knowledge of the different factors involved increases, it will probably be completely subdivided. (3) Hypertension associated with various diseased conditions, such as Graves' disease, myxedema, adrenal tumors, valvular heart disease, arteriovenous aneurysm and atherosclerosis of the aorta.

increases—from 9 per cent in the age group between forty and forty-nine years up to 58 per cent in those over eighty years of age. That the systolic type of hypertension is chiefly associated with the older age groups is further shown by the fact that 73 per cent of the cases with elevated systolic and low diastolic pressures are found in the age groups above sixty years, while only 45 per cent of the entire number of hypertensives (irrespective of the diastolic pressure) are above sixty years.

TABLE I.—AGE INCIDENCE OF SYSTOLIC HYPERTENSION.

Age, yrs.	Hypertensives.		
	Total.	Systolic.	Total, per cent.
Below 40	15	0	0
40-49	34	3	9
50-59	83	15	18
60-69	70	29	41
70-79	23	12	52
Above 80	12	7	58
Total	237	66	28

This marked predominance of systolic hypertension among the older patients suggests three possible explanations: (1) That patients with high diastolic pressures die before reaching old age. (2) That as the hypertensives grow older there is a change in their type of hypertension, in that the diastolic pressure tends to become lower; this second possibility will be mentioned again when the kidney findings are discussed. (3) That systolic hypertension is a distinct phenomenon first appearing in old age.

Of the 66 cases, 16, or 24 per cent, were males and 50, or 76 per cent, were females. This corresponds very closely to the sex incidence among the entire hypertensive group of which 26 per cent were males and 74 per cent were females.

SYMPTOMS AND SIGNS. Only 14 out of the 66 patients complained of any of the symptoms commonly attributed to hypertension *per se*, for example, headaches, dizziness or throbbing sensations. In a few of the remainder there were cardiac symptoms, such as dyspnea, palpitation, or edema, but in the great majority there were no cardiovascular symptoms whatsoever, and the patients were totally ignorant of their high blood pressure until apprised of that fact.

On examination, the feature common to all of these patients was generalized arteriosclerosis. This was evidenced by palpable thickening and beading of the walls of the accessible vessels, arcus senilis, ophthalmoscopic changes, and signs of atherosclerosis of the aorta (widening of the area of aortic dullness, together with a harsh systolic murmur—in the absence of lentic aortitis—and at times atheromatous plaques on the Roentgen ray plate). In most of the cases the degree of sclerosis appeared to be quite marked.

TABLE II.—NECROPSY FINDINGS IN CASES OF SYSTOLIC HYPERTENSION.

No.	Age, yrs.	Blood pressure, mm. Hg.	Heart.		Coronary arterio-sclerosis.	Aorta.		Weight, gm. per pair.	Kidneys.			Remarks.
			Valves.	Muscle.		Athero-sclerosis.	Dilatation.		Gross appearance.	Arterio-sclerosis.	Glo-meruli.	
10152	87	190/70	Normal	Myocardial fibrosis	++	++	Slight dilatation	200	Finely granular	++	Normal	General and cerebral arteriosclerosis.
9746	80	210/60	Normal	++	++	Slight dilatation of arch	180	Finely granular	++	Normal	General arteriosclerosis.
8612	75	180/75	Normal	Myocardial fibrosis	++	++	320	Slightly granular	++	Normal	General arteriosclerosis.
3315	75	160/80	Arteriosclerotic leaflets thickened	+	++	150	Scarred	++	Fibrosis	General arteriosclerosis.
9985	74	210/91	Thickened leaflets	Myocardial degeneration	++	++	320	Slightly granular	++	Normal	General and cerebral arteriosclerosis.
13875	72	188/74	Normal	Myocardial fibrosis	+	++	215	Finely granular	++	Normal	General arteriosclerosis.
3253	65	190/92	Normal	Myocardial degeneration	++	++	390	Finely granular	++	Fibrosis	General arteriosclerosis.
10063	60	160/80	Normal	Myocardial fibrosis	++	++	Slight dilatation of arch	270	Scarred	++	Normal	General arteriosclerosis.
3501	55	240/100	Normal	Myocardial fibrosis	++	++	200	Scarred	++	Fibrosis	General arteriosclerosis.
9096	51	228/100	Normal	Myocardial degeneration	+	++	300	Smooth; congested	++	Fibrosis	General arteriosclerosis.

+ = slight degree.

++ = marked degree.

+++ = very marked or extreme degree.

Thirty-eight patients, or 58 per cent, showed roentgenologic or definite clinical signs of cardiac hypertrophy, although in a good many of these the hypertrophy was thought to be only slight.

The majority of these patients had systolic murmurs: A mitral systolic murmur in 28 cases, an aortic systolic in 9 and both of these murmurs in 17 cases. However, evidence of actual organic valvular defects was very rare in our series. There was only 1 case of mitral stenosis and another of combined aortic insufficiency and mitral insufficiency. The murmurs present in practically all of these cases were usually ascribed to so-called "relative mitral insufficiency" due to dilatation of the left ventricle, or to atherosclerosis and dilatation of the aorta.

As regards the state of compensation, 15 patients, or 23 per cent, had cardiac insufficiency, while 51 patients, or 77 per cent, were compensated.

There were 22 diabetics in the series (33 per cent), while the incidence of diabetes among the entire group of hypertensives was only 23 per cent. This slight increase in the proportion of diabetes among systolic hypertensives may be ascribed to the fact that our diabetics are largely recruited from the higher age groups, and also to the fact that the diabetes may have some influence on the sclerosis of the bloodvessels which is the condition common to all of these cases.

There were 15 cases of hemiplegia (23 per cent), while the incidence of hemiplegics in the entire group of hypertensives was only 14 per cent. The higher percentage here may perhaps once more be ascribed to the fact that hemiplegias occur more commonly among the older age groups.

CAUSES OF DEATH. Twenty-one of our patients died. Of these the cause of death was pneumonia (chiefly a terminal bronchopneumonia) in 6 cases, cardiac failure in 4, cerebral hemorrhage in 3, carcinoma in 2, uremia in 1, amyotrophic lateral sclerosis in 1, thromboangiitis obliterans in 1, and unassigned except for generalized arteriosclerosis in 3 cases. There was, therefore, no single cause or mode of death common to this group. This is contrary to the views of Stone,¹⁴ who held that patients with a low diastolic pressure died a "cardiac death" (myocardial exhaustion or angina pectoris), while those with a high diastolic pressure died a "cerebral death" (thrombosis and edema associated with disturbed renal function, or cerebral hemorrhage).

NECROPSY MATERIAL. Ten patients belonging to this group of high systolic with relatively low diastolic pressures came to autopsy. The necropsy protocols were carefully studied and the microscopic sections personally reexamined.

Heart. The heart weights varied between 300 and 450 gm. Six of the hearts weighed 400 gm. or less, while only 1 weighed more than 450 gm. The hypertrophy was, therefore, only moderate,

and in all of the cases it was manifested chiefly in the left ventricle. The heart valves were essentially normal in all cases, except for some atherosclerotic thickening of the leaflets. The cardiac muscle in 8 of the 10 cases showed definite degenerative changes, labelled by the pathologist in different instances as "myocardial fibrosis" or "myocardial degeneration." In 1 of the remaining cases the myocardium showed evidence of fatty infiltration, while in the other case there were very small scarred areas in the muscle. The heart muscle in most instances appeared to have an increased amount of fat, and was replaced in areas by linear streaks or irregular scars of glistening white fibrous connective tissue. These areas of replacement fibrosis were most commonly noted in the wall of the left ventricle near the apex, in the interventricular septum and sometimes in the papillary muscles of the left ventricle.

Coronary Arteries. Definite atherosclerotic changes were noted in the coronary arteries of all the hearts, and in most instances the degree of involvement was quite marked. The vessels were tortuous, their walls were thickened, and the intima was flecked with fatty and at times calcified plaques. In some places the lumen was dilated, while in others it was considerably stenosed, but in no one case was complete occlusion of a main trunk demonstrable, although in one instance a very careful search showed some of the smaller branches to be closed.

Aorta. All of the cases showed marked atherosclerosis of the aorta and in most instances the degree of involvement was extreme. In 3 of the cases there was a diffuse dilatation of the arch. In this connection it must be remarked that a considerable degree of dilatation of the aorta must be present before it is noted by the pathologist in his diagnosis, and it may be presumed, therefore, that more of these patients showed some dilatation of the aorta than the protocols mention. The aortas showed the typical picture of advanced atherosclerotic changes, the intima being involved, with changes ranging from fatty and waxy plaques to hyalinization, calcification and ulceration. The involvement was least marked at the base of the aorta, and became progressively more extreme on advancing downward toward the bifurcation. As the result of these atherosclerotic changes just described the elasticity was naturally very much impaired.

Kidneys. The kidney weights varied between 150 and 390 gm. per pair. In 6 cases the weight of the pair was less than 300 gm.; in 3 cases, between 300 and 320 gm.; in 1 case, 390 gm. The capsules were adherent in some cases, and stripped fairly easily in others. In all of the cases but 1 the kidneys presented what is commonly described as a finely granular external appearance. In addition, many of them showed large coarse irregular scarring. On cut section this scarring could readily be made out. The cortex was somewhat irregular and thinned in most instances, and the

striations had a tendency to be obliterated in parts. The kidney vessels were prominent, and the arcuate vessels especially were grossly thickened. On microscopic examination the walls of the arterioles were found thickened in all of the cases. The glomeruli were normal in some instances and fibrosed in others. The presence of evidence of arteriolosclerosis in all of these kidneys is in accordance with the findings in all cases of hypertension irrespective of the diastolic pressure,¹⁵ and may possibly indicate that these patients originally had high diastolic pressures also, but that as the main vascular trunks became sclerosed the diastolic pressure decreased.

GENERALIZED ARTERIOSCLEROSIS. All of the cases showed evidence of generalized sclerosis involving the vascular system throughout the body—including the brain in those cases in which that organ was included in the necropsy.

IMMEDIATE CAUSE OF DEATH. This varied widely in the different cases and appeared to have no great significance.

COMMENT. The question of the mechanism of the causation of this type of high blood pressure resolves itself into ascertaining whether: (1) Systolic hypertension originates as such, and therefore has its own distinct mechanism; or (2) it is merely one stage, either early or late, of true diastolic hypertension.

The arteriolosclerotic kidneys, similar to those found in diastolic hypertension would seem to favor the second theory. However, the advanced age of these patients is very much against an early stage, and in favor rather of a late stage of diastolic hypertension, since this usually begins to manifest itself before the age of sixty.

On the other hand, the fact that the cardiac hypertrophy is not marked in most of these cases, and is apparently absent in about half of them would argue against the hypothesis of a late stage of diastolic hypertension, as a long standing diastolic hypertension usually causes considerable cardiac enlargement. Also in the late stage of diastolic hypertension the kidneys are more contracted than those we find in systolic hypertension. Systolic hypertension is therefore not a late stage of diastolic hypertension.

We may compromise between the two main divergent views stated above and assume that systolic hypertension like diastolic hypertension is caused by some factor which brings about vasoconstriction of the peripheral vascular bed, but that in addition there is another factor—atherosclerosis of the larger arteries, which causes a low diastolic pressure. This explanation would account for the cases of marked atherosclerosis which do not show a hypertension, by assuming that they lacked the vasoconstricting factor.

It must be emphasized, however, that atherosclerosis of the aorta and systolic hypertension are not always concurrent phenomena, for, as is well known, patients with advanced aortic sclerosis may have normal blood pressures or even diastolic hypertension. The

interrelation of the many factors involved in the regulation of blood pressure is too complex to allow of ready explanations.

Conclusion. Patients with elevated systolic pressure and a relatively low diastolic pressure form a definite group characterized clinically by their 'relatively advanced age, by comparative infrequency of complaints directly referable to the hypertension, by generalized atherosclerosis with particular involvement of the aorta, by moderate cardiac hypertrophy in about half the cases, and by the presence of systolic murmurs over the mitral or aortic areas or both. In general they tend to run a benign and prolonged course.

At autopsy they show moderate cardiac hypertrophy, some degenerative changes of the heart muscle, atherosclerosis of the aorta and coronary arteries, kidneys which grossly appear finely granular with large scars and microscopically show arteriolosclerosis, and generalized arteriosclerosis of the entire vascular system.

The etiology of this type of hypertension cannot be determined as yet, but the sclerosis of the aorta and larger vessels is probably a factor.

These cases run a course and have a prognosis different from those with diastolic hypertension, in addition to having distinct clinical and pathological characteristics, and should, therefore, be differentiated and labelled as systolic hypertension.

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SALT-FREE DIET IN THE TREATMENT OF PRÆCLAMPTIC TOXEMIA.

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THERE is no subject in obstetric pathology clouded in greater mystery than the toxemias of pregnancy. This is especially true with respect to their etiology. That the symptom complex, præclampsia, is a manifestation of metabolic imbalance or auto-intoxication, is generally believed, but the factors influential in provoking the condition are wholly obscure. No causative toxin has thus far been isolated. Since præclampsia is regarded as an expression of a toxic process, the treatment commonly employed is in accordance with this hypothesis. Essentially, the treatment used is based upon elimination in the nature of purgation, sweating, diuresis, and venesection when indicated. In certain cases the termination of pregnancy was and still is practised. Invariably præclampsia is associated with renal damage and, hence, it has been assumed that it is accompanied by faulty elimination of toxic nitrogenous end products. Accordingly, the protein intake is usually restricted, depending upon the degree of præclampsia. In some cases the restriction of diet is practically a starvation regimen. Despite these measures præclampsia remains a disorder which is fraught with great danger to the expectant mother and her offspring.

At the suggestion of Dr. F. M. Allen, a salt-free diet was employed in the treatment of a series of præclamptic patients admitted to the Department of Obstetrics, Jefferson Medical College Hospital. Since the beginning of this investigation the researches of Harding and van Wyck,¹ as well as the work of de Wesselow and Wyatt,² have been published. Harding and van Wyck have shown in a series of 10 cases that the assumption that proteins play a rôle in the causation of præclampsia is unwarranted. Furthermore, Burger,³ proved by giving normal pregnant patients as high as 200 gm. of protein daily that the metabolism of these patients did not differ from that of nonpregnant patients. The latter conclusion coincides with our observation in that the nonprotein nitrogen, urea nitrogen and creatinin, were always found to be within normal bounds in the patients studied. The chief point to be derived from the work of de Wesselow and Wyatt is the emphasis with which

cyte count accompanied by a high lymphocyte count is a good prognostic sign. The appearance of a high polymorphonuclear leukocyte count together with a diminished lymphocyte count is generally considered to be due to secondary infection with pus-producing bacteria. This idea rests largely upon the fact that bacteriologic examinations of pulmonary cavities very commonly demonstrate the presence of cocci of one type or another.

Kalkbrenner² gives an excellent summary of the views of various authors on the significance of the blood picture in tuberculosis. He followed the blood picture carefully over a long period of time in 185 cases of pulmonary tuberculosis. His conclusions are very significant. A short abstract of his article follows: "To gain a proper perspective the blood count must be followed from the beginning to the end of the disease. The initial reaction is a lymphocytosis which remains high in direct proportion to the resistance of the individual. At the height of the pathologic process there is an increase of the polymorphonuclear leukocytes which remains in the active chronic forms. Pathologically this change is seen with bronchopneumonia, caseous pneumonia, cavity formation, extension of the process to other organs and in complications, such as grippe, typhus, and so forth. The worse the case the greater the increase of neutrophils and decrease of lymphocytes. With clinical improvement this picture is reversed. If the lymphocytes do not fall too low there is a possibility of the patient overcoming the infection. There are no sharp lines of distinction to be drawn in the interpretation of the blood picture. On healing, the blood picture returns to normal. All patients should have the advantage of thorough blood examinations. These with the help of other factors are of use in determining the phase of the disease and the method of treatment."

Spooner³ found no evidence of secondary infection in ten tuberculous kidneys surgically removed. His opening paragraph is so pertinent that it is here quoted *verbatim*. "For years, a popular belief has existed that the septic manifestations of tuberculosis were due to a mixed infection with pyogenic organisms, that cavities containing caseous and purulent material resulted from the action of such organisms. Leukocytosis in connection with tuberculous infection was supposed to result from this mixed infection; though at the present time Sahli is beginning to see light, when he states that the degree of such a leukocytosis is due to the intensity of the tuberculous process, rather than to invasion by any other organism."

In a study of the process of caseation¹ recently reported by one of us the time of appearance and the significance of the neutrophil, the mononuclear leukocyte and the lymphocyte in the tuberculous lesion was emphasized. The typical tubercle without giant-cell formation or caseation is the first reaction to the tubercle bacillus. This is formed by the mononuclear leukocytes with practically no participation of the neutrophil or the lymphocyte. If the infection

Laboratory Data. Hemoglobin, 76 per cent; erythrocytes, 4,450,000; leukocytes, 6800. Blood chemistry: Nonprotein nitrogen, 19.8; urea nitrogen, 10.6; creatinin, 1.4; sugar, 74; blood chlorids, 445.5 mg. per 100 cc. of blood. Composite urine: Specific gravity, 1010; faint trace of albumin; occasional hyalin casts; pus cells, 30 to 40 per low-power field. Blood Wassermann test + 3. Systolic blood pressure was 156 mm. and diastolic was 108 mm. on admission.

Subsequent Course. Routine treatment as outlined was prescribed. On October 23, ten days after admission, and after seven days of salt-free diet treatment, the systolic blood pressure was 108 mm., the diastolic 76 mm. and the patient was free symptomatically, as well as objectively, from complaints for which she was admitted. The patient requested her discharge from the hospital. She was delivered later by medical students. The final note was to the effect that the mother and child were doing well.

CASE III.—F. McL., aged thirty-three years, a multipara, was admitted to the Jefferson Hospital Maternity, October 9, 1925, in the eighth month of gestation, complaining of headache, dyspnea, edema of the legs, black spots before the eyes, dizziness and slight headache. The patient had been married for three years and had been pregnant before, the conception terminating in a stillbirth at the seventh month.

Physical Examination. There was slight edema of the face, the heart was slightly enlarged to the left and a mitral systolic murmur was present. The feet and ankles were edematous.

Laboratory Data. Hemoglobin 58 per cent; erythrocytes, 3,590,000; leukocytes, 6200. Blood chemistry: Nonprotein nitrogen, 36.58; urea nitrogen, 20.68; creatinin, 1.25; blood sugar, 83; plasma chlorids, 566.5 mg. per 100 cc. of blood. Phenolphthalein, 25 per cent first hour and 20 per cent second hour. Composite urine: Average specific gravity, 1013; decided trace of albumin, hyalin casts. Examination of the eye grounds by Dr. Heed revealed sclerosis of the retinal vessels. The systolic blood pressure on admission was 180 mm. and the diastolic 90 mm.

Subsequent Course. Treatment was followed as outlined. On October 21, twelve days after admission, the systolic blood pressure was 126 mm. and diastolic 68 mm., and the patient was free of all symptoms and objective signs complained of on admission, whereupon she insisted upon being discharged.

On November 11 the patient was readmitted and put on salt-free diet. During the first two weeks at home the patient followed instructions regarding the salt-free diet, which was later disregarded. On readmission the systolic blood pressure was 168 mm. and the diastolic 100 mm. On November 19 the blood pressure was 134 mm. systolic and 66 mm. diastolic. Labor ensued and the patient was delivered by forceps. Rectal anesthesia and morphin sulphate, hypodermatically, were employed. The child lived ten minutes after delivery. Postmortem, not including the brain and spinal cord, revealed the lungs only partially expanded and no evidence of toxic degeneration.

On the day following delivery the patient's face became edematous again. The blood chemistry studies showed marked nitrogenous retention; non-protein nitrogen, 92.3; urea nitrogen, 67.15; creatinin 2.8 mg. per 100 cc. of blood. Salt-free diet was maintained and on November 27 the blood chemistry was reported within normal bounds. On December 3 the chlorid estimate in the twenty-four-hour urinary output was reported as 0.264 gm. and the blood pressure was 120 mm. systolic and 72 mm. diastolic. The patient was discharged from the hospital, December 7, 1925.

CASE IV.—B. B., aged twenty-five years, in the seventh month of gestation, was admitted to the Jefferson Hospital Maternity on November 4,

1925, complaining of headache and dizziness, which had been present for from two to three months, and edema of the legs which became evident two weeks before admission. She had had scarlet fever at nine years of age, but otherwise her history was negative. Physical examination revealed a slight exophthalmus. The thyroid gland was symmetrically enlarged. The heart was normal in size and the rate averaged 100 per minute. Edema of the legs extended up to the knees.

Laboratory Data. Hemoglobin, 73 per cent; erythrocytes, 4,050,000; leukocytes, 8800. Blood chemistry: Nonprotein nitrogen 24.38; urea nitrogen, 9.52; creatinin, 1.41. Blood Wassermann test negative. Phenolphthalein, 40 per cent first hour and 15 per cent second hour. Composite urine: Specific gravity, 1008; cloud of albumin; occasional hyalin and granular casts; few pus cells. On admission the systolic blood pressure was 170 mm. and diastolic 110 mm.

Subsequent Course. Routine treatment as outlined was instituted, and the blood pressure remained systolic 168 mm. and diastolic 105 mm. for three days following admission. After four days of salt-free diet regime the blood pressure dropped to 150 mm. systolic and 80 mm. diastolic. On November 13 premature labor ensued and the patient was delivered of twins. The first of the twins weighed 4 pounds 8 ounces and is living and well. The second of the twins, a stillbirth, weighed 18 ounces and was delivered by version forty-five minutes after the first child. The patient was discharged on November 28, 1925, the blood pressure at that time being 120 mm. systolic and 80 mm. diastolic. The final note was to the effect that mother and child were doing well.

CASE V.—L. D. aged twenty-one years, unmarried, in the ninth month of gestation, was admitted to the Jefferson Hospital Maternity on December 1, 1925, complaining of headache and precordial distress. Physical examination: Her face was slightly edematous. The heart was normal in size, but the aortic sound was markedly accentuated.

Laboratory Data. Hemoglobin, 85 per cent; erythrocytes, 4,710,000; leukocytes, 9200. Blood chemistry: Nonprotein nitrogen, 24.19; urea nitrogen, 10.79; creatinin, 1.21; blood chlorids, 471 mg. per 100 cc. of blood. Blood Wassermann test negative. Phenolphthalein, first hour 30 per cent and second hour 20 per cent. Composite urine: Specific gravity, 1012; trace of albumin and granular casts. Modified Mosenthal test: Specific gravity ranged from 1012 to 1026. The eye grounds were normal. Blood pressure on admission was 158 mm. systolic and 60 mm. diastolic.

Subsequent Course. The blood pressure and clinical symptoms were not influenced by rest in bed. With salt-free diet the clinical symptoms complained of disappeared and the blood pressure returned to normal after one week. Spontaneous delivery occurred January 2, 1926, resulting in the birth of a normal child. The mother and child were discharged in good condition on January 18.

CASE VI.—A. C., aged forty-one years, in the ninth month of gestation, was admitted to the Jefferson Hospital Maternity, December 16, 1925, in a very restless state; she complained of marked dyspnea, dimness of vision and occasional fainting spells. She had had scarlet fever during childhood. She had had 8 children, 7 of whom were living. On admission her face, hands and legs were markedly edematous, the conjunctivæ were injected, the thyroid gland was slightly enlarged, and the heart was enlarged to the left.

Laboratory Data. Hemoglobin, 80 per cent; erythrocytes, 4,010,000; leukocytes, 7000. Blood chemistry: Nonprotein nitrogen, 18.7 urea nitrogen, 7.84; creatinin, 1.2. The blood Wassermann test was negative.

Phenolphthalein, 20 per cent first hour and 10 per cent second hour. Composite urine: Specific gravity, 1012; trace of albumin; hyalin casts. Modified Mosenthal test: Specific gravity varied from 1010 to 1025. Examination of the eye grounds by Dr. Heed revealed the veins slightly dilated. On admission the patient's systolic blood pressure was 210 mm. and diastolic 96 mm.

Subsequent Course. As the patient's condition was desperate; salt-free diet treatment was instituted at once. On the evening following admission the systolic pressure was 150 mm. and the diastolic 80 mm. The patient's general condition was improved and the edema had lessened, although this was not attributed to the treatment. Two days later the blood pressure rose to 190 mm. systolic and 120 mm. diastolic. On the third day after admission a phlebotomy was performed and 850 cc. of blood was removed. Following this the blood pressure was 180 mm. systolic and the diastolic remained unchanged. On December 22, at 6.15 A.M., six days after admission, labor ensued, with the birth of a stillborn child. Postmortem examination of the child revealed definite evidence of toxic degeneration.

It is of interest to note that on salt-free diet the patient lost 6 pounds during the first four days after admission.

The diet was maintained throughout the puerperium, which was uneventful. During this period the urine revealed traces of albumin and occasional hyalin casts. The patient was discharged from the hospital on January 5, 1926, the blood pressure at that time being 144 mm. systolic and 104 mm. diastolic.

It is obvious that on admission eclampsia was imminent in this case. Because of salt-free diet it was possible to avoid a Cesarean section, which was seriously considered at one time. The phlebotomy did not influence the symptoms.

CASE VII.—S. G., aged twenty-two years, a primipara in the sixth month of gestation, was admitted to the Jefferson Hospital Maternity on December 23, 1925, complaining of headache, dyspnea and generalized edema, which had been present for two weeks. The striking feature in the physical examination was the generalized edema.

Laboratory Data. Hemoglobin, 65 per cent; erythrocytes, 3,300,000; leukocytes 12,000. Blood chemistry: Nonprotein nitrogen, 27.02; urea nitrogen, 11.76; creatinin, 1.38. The blood Wassermann test was negative. Phenolphthalein, 25 per cent first hour and 15 per cent the second hour. Composite urine: Specific gravity, 1010; distinct trace of albumin; hyalin and granular casts. Modified Mosenthal test: Specific gravity varied from 1008 to 1018. Eye grounds appeared normal. Blood pressure on admission was 192 mm. systolic and 122 mm. diastolic.

Subsequent Course. After three days in bed on house diet the symptoms were not influenced, and the blood pressure remained practically unchanged. On salt-free diet and permitting the patient the freedom of the ward the clinical symptoms were completely controlled. There was a loss of 8 pounds of weight in five days. The blood pressure, however, was little influenced. Labor ensued on January 1, 1926, and after sixteen and a half hours, resulted in a stillbirth. Salt-free diet was continued during the puerperium, which was uneventful, and the patient was discharged from the hospital on January 14. The blood pressure was 110 mm. systolic and 84 mm. diastolic. Consent for postmortem examination on the child was refused.

CASE VIII.—L. W., aged twenty-seven years, in the eighth month of gestation, was admitted to the Jefferson Hospital Maternity on February 3, 1926, complaining of severe headache and dyspnea. She had 3 living children and also had had 1 miscarriage. On admission her face was

edematous. The heart was enlarged to the left, and the heart sounds were both accentuated.

Laboratory Data. Hemoglobin, 94 per cent; erythrocytes, 4,970,000; leukocytes, 9800. Blood chemistry: Nonprotein nitrogen, 19.34; urea nitrogen, 6.65; creatinin, 1.42; plasma chlorids, 528 mg. per 100 cc. of blood. The blood Wassermann test was negative. Van den Bergh test, negative. Composite urine: Average specific gravity, 1012; trace of albumin; occasional hyalin casts. Modified Mosenthal test: Specific gravity varied from 1012 to 1022. Eye grounds were normal. On admission the systolic blood pressure was 150 mm. and the diastolic 112 mm.

Subsequent Course. The average blood pressure after three days in bed and house diet was systolic 156 mm. and diastolic 98 mm. Salt-free diet was then instituted. The patient was discharged from the hospital on February 20, symptom-free, and the blood pressure was 112 mm. systolic and 84 mm. diastolic. The patient was given instructions to follow the salt-free diet.

On February 24 the patient returned to the hospital, and on February 25 labor ensued, resulting in the birth of a normal child. She was subsequently discharged from the hospital in good condition, as was her child.

CASE IX.—C. P., aged twenty-one years, a primipara, in the eighth month of gestation, was admitted to the Jefferson Hospital Maternity on May 20, 1926, complaining of headache, dimness of vision and edema of the legs. The headaches had persisted from the beginning of pregnancy. She stated that she had "kidney trouble during childhood." Physical examination on admission: The face was edematous; the heart was normal with the exception of a marked accentuation of the aortic sound; the legs were edematous.

Laboratory Data. Hemoglobin, 64 per cent; erythrocytes, 3,450,000; leukocytes, 8300. Blood chemistry: Nonprotein nitrogen, 30.30; urea, nitrogen, 13.04; creatinin, 1.6. The Wassermann test was negative. Composite urine: Specific gravity, 1008; light cloud of albumin and few hyalin casts. Modified Mosenthal test: Specific gravity varied from 1010 to 1018. The van den Bergh test was negative. The eye grounds were normal. The blood pressure on admission was 180 mm. systolic and 120 mm. diastolic.

Subsequent Course. Routine treatment as outlined was prescribed. The average blood pressure for three days was 178 mm. systolic and 106 mm. diastolic. The clinical symptoms remained unimproved. After two days on salt-free diet a distinct clinical improvement was noted. On May 28, eight days after admission, and after five days of salt-free diet, the blood pressure was 130 mm. and 80 mm. diastolic, and all clinical symptoms complained of on admission were relieved. From May 28 until June 9, when labor ensued, the systolic blood pressure varied from 130 mm. to 170 mm. and the diastolic from 94 mm. to 112 mm. There was a loss of 11 pounds in weight from May 23 until the time of delivery, on June 9. Labor resulted in the birth of a normal child weighing 7 pounds 2 ounces. Salt-free diet was discontinued during the puerperium, but was resumed on the eighth day due to the rise of blood pressure and the appearance of albumin and granular casts in the urine. On June 26, the patient was discharged from the hospital with a normal blood pressure.

CASE X.—M. McC., aged forty-one years, in the eighth month of gestation, was admitted to the Jefferson Hospital Maternity on May 8, 1926, complaining of severe headaches, dimness of vision, dyspnea and severe precordial distress. The headaches were present from the first month of pregnancy. She had had 4 children, all living and well. On admission

the patient's face was edematous; there was a marked pulsation in the root of the neck; the heart sounds were markedly accentuated.

Laboratory Data. Hemoglobin, 80 per cent; erythrocytes, 4,200,000; leukocytes, 6000. Blood chemistry: Nonprotein nitrogen, 21.42; urea nitrogen, 7.44; creatinin, 1.2. The blood Wassermann test was negative. Van den Bergh test, negative. Composite urine: Specific gravity, 1010; very faint trace of albumin; occasional hyalin cast. Modified Mosenthal test: Specific gravity varied from 1002 to 1010. Examination of eye grounds by Dr. Heed revealed slight fullness of the veins. The blood pressure on admission was 150 mm. systolic and 76 mm. diastolic.

Subsequent Course. No improvement was noted after three days on the outlined plan of treatment. After institution of the salt-free diet, allowing the patient the freedom of the ward, the blood pressure dropped to 110 mm. systolic and 60 mm. diastolic in one week, with relief from all the clinical symptoms complained of on admission. During the first five days while on salt-free diet there was a loss of 5 pounds in weight. Labor ensued on July 4, resulting in the birth of a child weighing 9 pounds 6 ounces. The mother and child were discharged from the hospital July 16, in good condition.

CASE XI.—A. G., a primipara, aged thirty-three years, in the sixth month of gestation, was admitted to the Jefferson Hospital Maternity on March 26, 1926, complaining of severe headache, edema of the face, and attacks of vomiting. Although she was married seventeen years, this was her first pregnancy. Nausea and vomiting developed during the second month of pregnancy and was persistent. The patient's face was quite edematous. The edema became evident two weeks before admission.

Laboratory Data. Hemoglobin, 80 per cent; erythrocytes, 4,150,000; leukocytes, 11,600. Blood chemistry: Nonprotein nitrogen, 18.34; urea nitrogen, 5.62; creatinin, 1.72; sugar 90 mg. per 100 cc. of blood. The Wassermann test was negative. Van den Bergh test, negative. Phenolphthalein, 30 per cent first hour and 30 per cent second hour. Composite urine: Specific gravity, 1005; faint trace to a cloud of albumin; hyalin casts. Modified Mosenthal test: Specific gravity varied from 1002 to 1010. Blood pressure on admission was 176 mm. systolic and 98 mm. diastolic.

Subsequent Course. The patient was placed on a salt-free diet immediately on admission since the symptoms were urgent. On April 11, the patient was discharged from the hospital free of all clinical symptoms, with a systolic blood pressure of 130 mm. and diastolic reading of 90 mm. The chlorid excretion for twenty-four hours at this time was below 1 gm. It is interesting to note a loss of 9 pounds in weight while on salt-free diet treatment.

On May 19 the patient was readmitted to the hospital, complaining of severe headache. The systolic blood pressure was 160 mm. and the diastolic 100 mm. The nonprotein nitrogen was 28; creatinin 1.8 mg. per 100 cc. of blood. The patient was placed on salt-free diet. The clinical symptoms improved during the first three days, and the average blood pressure was 160 mm. systolic and 100 mm. diastolic. On the fourth day following admission, at 9 p.m., the patient was seized with violent epigastric distress, associated with excruciating headache. There was a rise of blood pressure to 200 mm. systolic and 120 mm. diastolic. Abdominal Cesarean section resulted in the delivery of a 2 pound child, which lived four hours. Recovery of the mother was uneventful, excepting for occasional epigastric distress. On the day following the operation the urea nitrogen was 13.69; creatinin, 1.41; plasma chlorid, 671 mg. per 100 cc. of blood. The patient was discharged from the hospital four weeks later with a normal blood pressure.

CASE XII.—L. F., aged sixteen years, a primipara, in the seventh month of gestation, was admitted to the Jefferson Hospital Maternity on

June 29, 1926, complaining of severe headache and dimness of vision which had persisted since the second month of pregnancy. On admission it was noted that the patient was quite pale, the eye lids were edematous and the conjunctivæ injected. The heart was normal in size. Edema of the legs extended several inches above the knees.

Laboratory Data. Hemoglobin, 58 per cent; erythrocytes, 3,100,000; leukocytes, 8600. Blood chemistry: Nonprotein nitrogen, 30.44; urea nitrogen, 13.1; creatinin, 1.56 mg. per 100 cc. of blood. The Wassermann test was +1. Phenolphthalein, 8 per cent first hour and 20 per cent second hour. Composite urine: Heavy cloud of albumin; occasional hyalin casts; specific gravity, 1010. Modified Mosenthal test: Specific gravity varied from 1004 to 1020. The eye grounds on examination were rather pale and the veins were slightly dilated. The blood pressure on admission was 132 mm. systolic and 78 mm. diastolic.

Subsequent Course. The patient demonstrated once more that mere rest in bed on a house diet does not influence the course of the symptom complex of preëclamptic toxemia. On the contrary, on a salt-free diet the symptoms began to improve immediately. There was a drop of blood pressure and also a coincident loss of 10 pounds in weight until the time of delivery, July 25.

On July 25, after fourteen hours of active labor, the patient was delivered of twins by use of forceps. Ether anesthesia was used. The first child weighed 4 pounds and is living and well. The second child weighed 1 pound and was stillborn. Forty-eight hours after delivery the mother's temperature rose and her condition became alarming. On July 31 *Streptococcus hemolyticus* was isolated from the blood stream. Acute endocarditis supervened. The patient insisted on leaving the hospital on August 29. Death occurred two days later at her home.

CASE XIII.—M. H., aged thirty-eight years, in the ninth month of gestation, was admitted to the Jefferson Hospital Maternity on June 23, 1926, complaining of severe headache, dizziness, dimness of vision and precordial distress which had persisted for seven months. She was married at sixteen years of age and had had 5 pregnancies, 1 resulting in a stillbirth. A note from her physician, Dr. H. B. Ulmer, stated that she "was at full term and not in very good condition, having a blood pressure hovering around 200 mm. systolic and that during and since her last pregnancy, in 1923, her blood pressure averaged 180 mm. systolic." There was no history of hypertension in the family. Physical examination on admission: The patient's expression was one of anxiety; there was edema of the face and eyelids; a vigorous pulsation was obvious at the root of the neck; the lungs were clear; the apex impulse of the heart was in the fifth left interspace 12 cm. to the left of the midsternal line; a systolic shock was present; a loud systolic murmur was heard at the apex; there was no visible edema of the extremities.

Laboratory Data. Hemoglobin, 82 per cent; erythrocytes, 4,260,000; leukocytes, 7400. Blood chemistry: Nonprotein nitrogen, 29.12; urea nitrogen, 15.46; creatinin, 1.36. The blood Wassermann test was negative. Composite urine: Specific gravity, 1012; albumin, a cloud; occasional hyalin and granular casts. The modified Mosenthal test averaged in specific gravity 1002 to 1030. The eye grounds revealed nothing abnormal. On admission the systolic blood pressure was 180 mm. and the diastolic 110 mm.

Subsequent Course. Routine treatment in bed resulted in no improvement of the clinical symptoms. On salt-free diet, permitting the patient the freedom of the ward, there was a striking improvement after three days. There was a weight loss of 12 pounds. Labor ensued on July 16, was

uneventful, and resulted in the birth of a child weighing 8 pounds 10 ounces. The mother was discharged from the hospital on July 25, the blood pressure at that time being 110 mm. systolic and 70 mm. diastolic, and her general condition good, as was that of her infant.

CASE XIII TYPICAL OF THE PROGRESS OF EVENTS OBSERVED IN THE PATIENTS STUDIED.

Date 1926.	NaCl in diet, gm.	Urine.			Plasma NaCl mg. per 100 cc.	Blood urea nitrogen mg. per 100 cc.	Blood pressure.				Weight, pounds.
		Vol., cc.	NaCl, per cent.	Total NaCl, gm.			A.M.		P.M.		
							S.	D.	S.	D.	
June 23	House diet	180	110	184
24*	530	11.33	150	106	172	100	
25	174	100	146	80	
26	Salt-free diet	154	90	144	84	179½
27	132	70	182	110	
28	...	1000	0.692	6.92	150	100	138	100	
29	...	960	0.507	4.86	140	100	134	92	
30	130	88	124	90	173½
July 1	...	610	0.626	3.81	110	70	
2	...	270	0.593	1.60	116	78	110	88	
3	...	250	0.223	0.55	130	90	136	98	173
4	110	86	122	90	
5	...	950	0.169	1.60	110	78	130	80	
6	...	240	0.136	0.32	90	60	110	64	174
7	...	740	0.210	1.55	116	60	104	70	
8	...	545	0.157	0.85	110	80	90	56	
9	...	615	0.115	0.70	110	60	173
10	...	465	0.235	1.09	120	80	112	70	
11	...	645	0.091	0.58	120	78	90	58	
12	...	590	0.169	0.99	116	70	110	64	172½
13	...	690	0.210	1.44	100	70	98	64	
14	...	590	0.181	1.06	90	48	90	60	
15	...	525	0.144	0.75	100	68	100	48	
16†	...	610	0.111	0.67	150	98	120	80	
17	110	60	
18†	15.46	120	60	
28	118	70	

* Creatinin, 1.45; nonprotein nitrogen, 23.77.

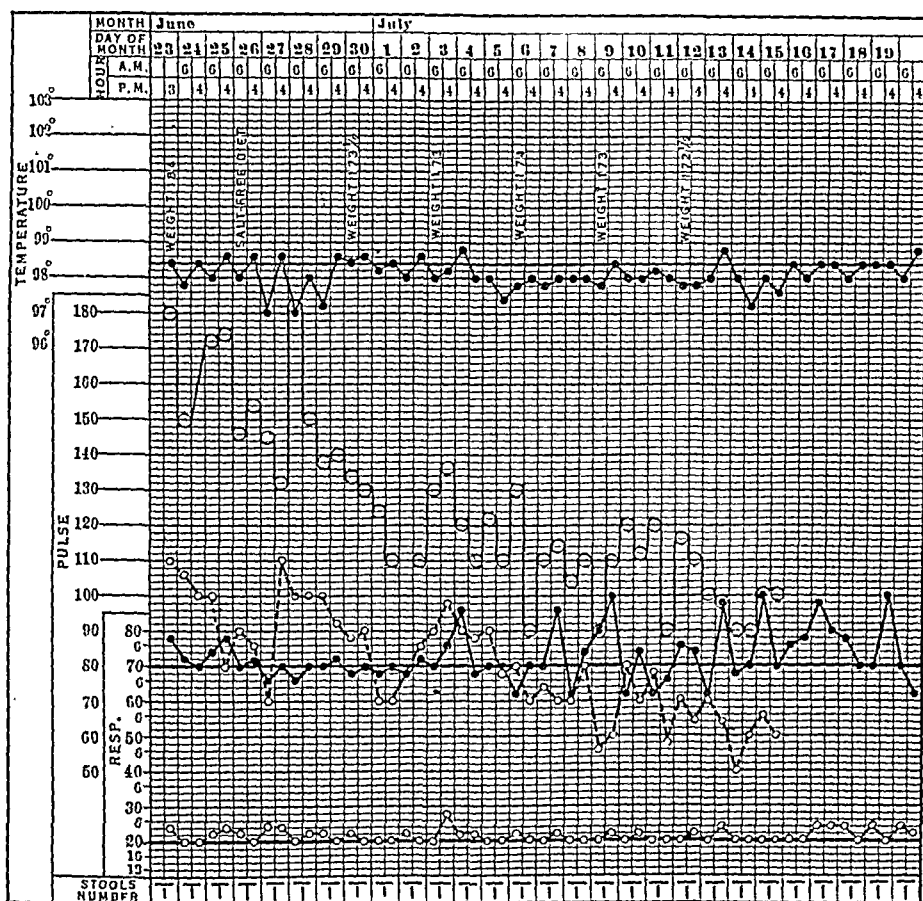
† Labor.

‡ Creatinin, 1.36; nonprotein nitrogen, 29.12.

Comment. Thirteen patients with preëclamptic toxemia were studied. Twelve of the mothers are alive. One mother died two months following delivery; the cause of death was septic endocarditis. Of the 15 children there were 2 sets of twins. There was 1 miscarriage. Four were stillborn. One child whose death was not caused by toxemia, as proved by postmortem examination, lived for ten minutes after delivery. One child died four hours following delivery; it was delivered by Cesarean section, and weighed 2 pounds. Eight children are living and well.

Certain observations have been made in the course of the foregoing studies:

1. The blood pressure as a rule was found to be considerably above normal limits.



CLINICAL RECORD OF CASE XIII.

2. The blood pressure was not influenced by rest in bed on a house diet. The opposite was true when the patients were placed on a salt-free diet, despite the fact that they were permitted the freedom of the ward. In every patient under observation there was a drop of blood pressure to normal with the exception of Cases VI and VII. Although the blood pressure in these 2 patients was not influenced there was a decided improvement in the clinical symptoms, together with complete disappearance of the edema.

3. The study of the blood with regard to the nonprotein nitrogen, urea nitrogen, and creatinin was always found normal. In nephritis, on the contrary, the one phase that stands out in bold relief is the blood chemistry. There is a definite retention of toxic nitrogenous end products.

4. Examination of the blood chlorides proved of no value from a standpoint of diagnosis. They were always found within normal limits, regardless of the severity of the symptoms and the degree of edema. The chlorid content in the twenty-four hour urinary output serves as a criterion in the treatment. The success of the treatment depends upon maintaining the urinary chlorid output not above 1 gm.

5. The composite urinary analyses of the patients studied had shown that there was albumin and casts, either hyalin or granular or both, present. On the salt-free diet the patients invariably had shown an improvement varying from entire disappearance of the albumin, where a heavy cloud was reported on admission, to a trace after the patient was on salt-free diet for a few days. Furthermore, subsequent urinary examination showed a marked diminution in the number of casts.

6. The blood sugar, phenolphthalein excretion, modified Mosen-thal tests, and eye ground examinations were made a routine procedure, but did not prove to be of any clinical value.

7. One incident, not without significance, is the loss of weight experienced by these patients on the salt-free diet. This loss is essentially not a loss of flesh, but due to fluid loss from the tissues.

Although conclusive deductions as to the value of salt-free diet in the treatment of præclampsia obviously cannot be made from the small number of patients observed, yet the employment of this method is urged. The results obtained in the treatment of the 13 patients herein recorded seem to indicate that this method is superior to other measures heretofore employed.

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A STUDY OF ILL EFFECTS FROM LUMBAR PUNCTURE, WITH REPORT OF A POSTPUNCTURE FATALITY.*

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A REVIEW of the literature concerning lumbar puncture strikes one with the preponderance of attention given the attendant inconveniences and dangers occasionally resulting from the procedure

* Studies and contribution of the Department of Dermatology and Syphilology of the University of Michigan, Service of Dr. Udo J. Wile. Contributed by the author to the sixtieth anniversary volume for Dr. Aldred Scott Warthin.

over that bestowed upon its diagnostic and therapeutic values. Undoubtedly, the tendency to stress its dangers was actuated by the early fatalities encountered in the puncture and drainage of cases of brain tumor. The first of this series was contributed by Fürbringer,¹ who described 3 such cases in publications appearing within five years after the description of the technique for diagnostic lumbar puncture by Quincke.²

Twenty years after Fürbringer's first reports, Schönbeck³ was able to collect 71 cases of fatality following lumbar puncture. It is highly improbable that the above figures represent even an approximate of the total cases up to that time, due to the failure to publish these occurrences. In fact, Reichmann⁴ suggests that only about 10 per cent of the actual cases are recorded. Schönbeck presents an interesting analysis of the fatal cases from the standpoint of the type of disease which the patients presented. This analysis is substantiated by autopsy findings in the large majority of his cases.

Of the 71 cases considered by Schönbeck, 37 presented intracranial tumors, 13 recent cerebral hemorrhages, 7 meningitis of various types 4 were uremic, 2 presented cysticercus and 1 echinococcus cysts, 1 acute myelitis, 1 abscess of the cerebellum with rupture into the cranial cavity and localized meningitis, 1 a child with rickets and pneumonia, 1 with compression of the cervical spinal canal from tumor and 1 with cerebral anemia and pulmonary edema following chloroform administration. Two other cases presented elongation of the cerebellar processes, producing pressure of the medulla against the foramen magnum, 1 apparently being due to severe hydrocephalus, the other presenting only a moderate dilatation of a lateral ventricle.

Of the 7 cases with meningitis, 2 were tuberculous, 2 were purulent in type with a third accompanied by sinus thrombosis, 1 pneumococcic and 1 presumably meningococcic in type. Of the cases with tumors, 7 involved the cerebellum, 6 the frontal lobe, 4 the temporal lobe, 1 the occipital lobe, 1 both the frontal and parietal lobes, 1 involved the pons, 1 the hypophysis, 1 the internal capsule, 5 involved the ventricles, 1 the aqueduct and the remainder were in regions less specifically stated. The cases of hemorrhage occurred in three patients with ruptured cerebral aneurysms, in 2 with hemorrhage from apoplexy into the ventricles, in 3 with cases of fresh apoplexy, 1 with recurrent fever, the other 2 with nephritis, 1 case of intradural hemorrhage with hydrocephalus, 1 case in which rupture of a vessel in the fossa of Sylvius followed brain puncture, 2 cases of skull fracture and 1 case with cerebral arteriosclerosis with suspected hemorrhage without autopsy findings.

The chronologic relation of the spinal puncture and the death of the patient is a markedly variable factor in these cases and throughout the series this ranges from simultaneous exitus to death

occurring thirteen days after the puncture was performed. Likewise, the amount of fluid withdrawn varied considerably, in some cases the needle being withdrawn without the removal of any fluid, while in others as much as 75 cc. was drawn off. In 15 cases 5 cc. or less was removed.

In the majority of the cases the patients complained of severe headache following the lumbar puncture, later followed by coma and respiratory failure. It is apparent from the length of the interval between the puncture and ensuing death that in the cases in which this period was longest the direct relationship between the two events must be regarded as questionable.

Unfortunately in the majority of cases the position of the bulb in relation to the occipital foramen and the presence or absence of the spinal fluid in normal amounts was not determined at the necropsies, which makes the establishment of a direct relation between puncture and subsequent death even more difficult. As has frequently been pointed out, death in cases of brain tumor may be sudden and without apparent immediate cause, and it seems entirely probable that in many of these cases the relation is coincidental rather than one of cause and effect.

Based on personal experiences, various authorities express widely differing opinions as to the advisability of performing a spinal puncture in cases of suspected brain tumor. Apparently a majority of writers accept the conservative viewpoint of admitting an element of danger in cases in which brain tumor has been demonstrated. Further, a wide divergence of opinion exists as to the cause of postpuncture headache. Various authors regard this as psychogenetic (Eichelberg and Pförtner⁵). Kaiser⁶ regards the untoward psychic effect in certain cases, as a contraindication to lumbar puncture, and states that its ill effects must be compensated for by the diagnostic benefit to be derived from the procedure.

Views on the organic causes of postpuncture headache are numerous, but with a few exceptions are based on the supposition of leakage of the spinal fluid subsequent to the puncture or removal of too great a quantity of the fluid. Expressing a different view, Walter⁷ believes the headache to be the result of a reflex from the lumbar puncture wound of the dura. Reichmann⁸ believes that hyperemia of the meninges due to removal of the fluid is responsible.

MacRoberts⁹ advances the ingenious theory that the headache is due to pressure of the weight of the brain on the basilar meninges caused by loss of the water cushion resulting from the lumbar puncture, as well as to rise of intracranial venous pressure caused by obstruction of the basilar venous plexus by the weight of the brain when this water cushion is absent. By this explanation he accounts for the orthostatic feature of the headache. He explains the headache, in cases where no fluid is removed, on the basis of undetected postpuncture leakage.

The question as to whether this leakage commonly occurs is a much debated one. Weed¹⁰ and his coworkers showed that particles of lampblack injected into the dural cavity of laboratory animals later could be found in the extradural soft tissues. Of more interest, as regards conditions in the human form, is a communication to the author by Dr. H. C. Solomon, who states that he has examined Roentgen ray plates taken forty-eight hours after intradural injection of lipiodol and that these definitely show that the substance has invaded the epidural space, apparently flowing through the opening made by the needle employed. Experiments on cadavers by Ingvar¹¹ showed that methylene blue perfused into the cranial cavity ultimately found its way into the epidural space following lumbar puncture. In substantiation of this also is the fact that in some of the cases reviewed by Shönbeck¹² evidence of extensive leakage was noted on postmortem examination.

Opposed to the theory of leakage as a cause of the untoward effects of lumbar puncture is the fact that the cerebrospinal fluid is known to be rapidly secreted as observed in cases presenting abnormal communications between the dural canal and the surface, such as in skull fracture. However, in these cases it has been pointed out that the fluid is being liberated under conditions of greatly reduced intracranial pressure and, therefore, much more rapidly than in the normal subject. Be this as it may, it is highly probable that a persistently patent puncture wound causes an actual disturbance of the equilibrium of intracranial pressure. It has been demonstrated by Weed¹³ and his collaborators that such an equilibrium exists between the arterial, venous and cerebrospinal fluid systems and that a disturbance in one is compensated by changes in the others. In this way, withdrawal of the spinal fluid produces meningeal hyperemia, which has been produced artificially in laboratory animals (Ossipow¹⁴), as well as noted in man.

As illustrating the possibility of postpuncture leakage of the cerebrospinal fluid with fatal termination, the following case is presented:

Case Report.—Mrs. N. F., a switchboard operator, aged thirty-three years, divorced, presented herself at the University Hospital, Department of Dermatology and Syphilology, on February 16, 1925, for examination for syphilis. This condition was first discovered by a local health officer by means of a blood test, taken as a result of the patient being referred for general examination at the request of a social investigator, whose services had been attracted by the fact that the patient was unable to care for her household. In the clinic she complained only of nervousness and adynamia. The family history revealed nothing of value. The marital history showed that the patient had been married at the age of eighteen, had lived with her husband for eight years, and had then separated. She did not know whether her husband had had syphilis. There were five pregnancies. The first resulted in self-induced abortion, while the other four terminated normally. These children are considered normal by the patient, and were known to have negative Wassermann tests.

In her past history she gave the information that she had had measles in childhood, but knew of no other definite illnesses. There was no history of gonorrhea. Questioning as to the present illness revealed that the patient had not suspected the nature of her condition. She had at no time noticed a genital sore, nor had she ever noted an eruption, mucous membrane lesions, nor alopecia suggesting secondary syphilitic involvement. For two months before entering the hospital she had suffered from progressive weakness manifested in an inability to do her routine work. This was accompanied by nervousness and increased irritability, and because of the fact that she detained a daughter, aged thirteen years, at home to aid in her housework, the investigation mentioned above was ordered. There was no history of antisyphilitic therapy in any form.

Physical examination revealed the patient to be a poorly nourished, rather cachectic woman, whose physiologic age was obviously greater than her chronologic age. She presented a definite pallor, and the color of the skin is best described as sallow. The hair showed a marked absence of the normal luster. The pupils were equal in size and, although slightly irregular in outline, reacted normally to light and in accommodation. The mucosæ were negative except for the generalized pallor. There was a generalized average pea-sized lymph adenitis affecting all glands available to palpation. The heart and lungs were clinically normal. The spleen and liver could not be palpated. The bones and joints presented no definite abnormalities. Neurologic examination was negative, except for some exaggeration of the tendon reflexes. The routine blood Wassermann test was returned as 4+.

Antisyphilitic treatment was advised, and on the afternoon of February 18 an intravenous injection of 3 deg. of neocarsphenamin was given. Within two hours of this procedure, as is routinely done, a diagnostic lumbar puncture was performed and about 5 cc. of fluid withdrawn. Examination of this showed 37 lymphocytes per cubic millimeter, with a slight increase in the globulin and albumin. The Wassermann test here too was found to be 4+ positive. The gold sol curve was 11122110000 and the mastic 344320.

Following the puncture, which was performed without difficulty in the sitting posture, the patient was immediately confined to bed with the foot of the bed elevated for the ensuing six hours. The following morning upon sitting up she complained of some dizziness and nausea. Because of this she remained in bed and the elevation of the foot of the bed was resumed. On the following morning she felt somewhat better and sat up in bed the early part of the day. There was still some dizziness, but the nausea had disappeared and the patient was able to take liquid food. During the late afternoon she became stuporous and examination revealed lateral nystagmus with some spasticity of the extremities and increase in all tendon reflexes. However, neither Kernig's nor Babinski's signs were obtained and there was no rigidity of the neck. The patient became comatose and the temperature subnormal. During the last four hours of life the temperature rose to 101.6°, the pulse to 125 and the respirations to 38. In the last half hour the pulse became too rapid to count, the respirations more rapid and shallow and the patient died at 1.15 A.M., February 21. A fundus examination about eight hours antemortem revealed no lesions nor choking of the disks.

During the last hours of the patient's life she was turned on her side several times by the resident physician, in the process of extraction of mucus from the throat, and on none of these occasions was any gross tumescence of the soft tissues of the lumbar region noted.

An autopsy was performed about eight hours postmortem and through courtesy of the Department of Pathology the following significant positive findings are given:

Involving the entire lumbar region there was noted a massive tumescence about the region in which the puncture had been performed. Examination showed this to be due to an infiltration of fluid showing all the characteristics of the cerebrospinal fluid. The dural cavity was devoid of demonstrable fluid. However, in spite of this finding, a definite wound in the dura, as a result of the puncture, could not be found. The central nervous system presented marked changes. The spinal meninges showed active syphilitic meningitis with characteristic perivascular infiltration. The cord showed a syphilitic myelitis. The cerebral meninges showed localized thickenings with increased numbers of wandering cells, congestion and edema and perivascular plasma cell infiltrations. The brain substance showed scattered infiltrations of a similar nature, as well as congestion and edema. The choroid plexus showed focal perivascular infiltrations. The pituitary revealed in its anterior lobe almost complete replacement by scar tissue with persistent remains of atrophic parenchyma, with miliary gummas in all stages scattered throughout the scar tissue. There was found atrophy, passive congestion and parenchymatous degeneration of all organs with marked pulmonary edema. The patient's constitution was described as being of the thymicolymphatic, hypoplastic type.

Clinically, the cause of death in this case is obscure. The degree of meningeal as well as spinal and cerebral involvement is entirely compatible with life; in fact, as judged by all our diagnostic criteria, equally active cases are met with almost daily in whom there is little associated disability. That lumbar puncture alone is not sufficient to precipitate death in these cases is evident from the frequency with which it is done.

In the Department of Dermatology and Syphilology during the past fifteen years some 27,000 lumbar punctures have been performed, many of them in cases of cerebrospinal syphilis in late stages. In this entire group there occurred only the fatality herein described, and 1 in which a purulent meningitis developed subsequently. Vedel¹⁵ and his coworkers describe a case of death occurring four hours after lumbar puncture in a patient who had recently had an acute supposedly syphilitic meningitis. Unfortunately no autopsy was performed. These authors also mention 2 other cases of death following puncture in patients with general paralysis, 1 with syncope and the other with epileptiform seizures preceding death.

That leakage in all degrees may occur is shown by the evidence quoted above, and by this case, as well as by many cases of skull fracture. Whether leakage alone is sufficient to cause death is not a definitely settled question, although the fact that cranial leakage does not necessarily do so is well known.

Spinal leakage is held in a different light by Ingvar,¹⁶ and is thought of as causing an acute internal hydrocephalus in some cases because of the increased secretion of spinal fluid with resulting pressure upon the posterior part of the cerebellum and bulb, and because of the suction probably exerted upon the brain by the constantly lowered pressure in the spinal canal. Anatomic evidence was not forthcoming in the case here reported to establish it as

one in which death was caused by so-called plugging of the bulb into the foramen magnum.

The part played by the pituitary lesion is likewise obscure and, while the change in the patient's general condition can at least be ascribed to this in part, ascribing it as a cause of death in this case can only rest on conjecture until further investigative work is done on the subject.

Conclusions. 1. Routine lumbar puncture in the syphilitic patient is a comparatively safe procedure; death followed puncture in a ratio of less than 1 in 13,000 cases in this clinic. Of the 2 cases encountered only 1 could be definitely ascribed to the lumbar puncture (purulent meningitis).

2. In addition to aseptic technique, only routine precautions, such as subsequent rest in bed with elevation of the foot of the bed are necessary in spinal puncture of the syphilitic patient.

3. The case herein described is one presenting evidence of enormous postpuncture leakage of the spinal fluid.

4. The question of the relation of this leakage to the death of the patient is complicated by the evidence of syphilitic involvement of the central nervous system and by the thymicolymphatic constitution.

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REVIEWS.

THE PRINCIPLES AND PRACTICE OF ENDOCRINE MEDICINE. By WILLIAM NATHANIEL BERKELEY, PH.D., M.D., Attending Physician at the Good Samaritan Dispensary, New York; and one-time Director of the Laboratory of Experimental Medicine, Cornell University Medical College. Pp. 368; 56 engravings and 4 colored plates. Philadelphia: Lea & Febiger, 1926. Price, \$4.50.

THE chief value of this book lies in the fact that the writer's discussion of endocrine disorders is based upon the fundamentals of anatomy, physiology, and animal experimentation. This makes the work convincing, and gives the reader a sense of security, a state of mind not often aroused by the customary presentation of the subject. In the present uncertain state of our knowledge of endocrine diseases it is good to have the few established facts clearly stated as they are here. The writer is widely read, too, in the literature of his subject. Though condensed in form, the work is comprehensive in scope. Its sanity and intelligence make it a desirable volume for the practitioner's library.

T. M.

ELEMENTARY BACTERIOLOGY AND PROTOZOÖLOGY FOR THE USE OF NURSES. By HERBERT FOX, M.D., Director of the William Pepper Laboratory, University of Pennsylvania. Fourth edition revised. Pp. 242; 24 illustrations. Philadelphia: Lea & Febiger, 1926. Price, \$2.50.

THIS well-known book appears again in its newest edition altered to suit the ever growing scientific world yet in its essence much the same. Some chapters have been entirely rewritten as that on the "Relation of Bacteria to Disease and Immunity," others scarcely touched.

The binding is uniform with the series of which it is a part. Unfortunately the paper used is highly glazed making the text trying to read. This book has already found its place in the teaching of student nurses.

M. N.

THE DISEASES OF INFANTS AND CHILDREN. By J. P. CROZER GRIFFITH, M.D., PH.D., Professor of Pediatrics in the Graduate School of Medicine of the University of Pennsylvania, and A. GRAEME MITCHELL, M.D., Professor of Pediatrics, College of Medicine, University of Cincinnati. Second edition, reset. Two octavo volumes. Pp. 1715; 461 illustrations, including 20 plates in colors. Philadelphia and London: W. B. Saunders Company, 1927. Price, \$20.00 net.

THIS widely-known text has been rewritten with the aid of a coauthor to include the many important advances made in pediatric medicine since the original edition appeared eight years ago. This has enlarged the book from 1540 pages to 1845 pages including index.

The section on infant feeding, so important a part of any book on Pediatrics, has been enlarged, and discusses simple dilution feeding, acid milks, concentrated feeding and the Pirquet system. The chapter on the diet after the first year has happily been doubled in size. The newest researches on rickets and on scarlet fever are covered in the text.

This book occupies a position between that of a student text and that of a system of pediatrics. Its compactness adapts it to the practitioner's desk, while its wealth of reference commends it to the pediatricist of experience. One will find in this book either that for which he looks, or will find reference to an especially complete article upon the particular subject. To facilitate such search, a full index to both volumes has been included in each. The reviewer is particularly impressed by the completeness, clarity and order of this index. Another valuable feature is the frequency of cross reference within the text.

J. S.

A TEXTBOOK OF EMBRYOLOGY. By HARVEY E. JORDAN, A.M., PH.D., Professor of Histology and Embryology, University of Virginia, and JAMES E. KINDRED, M.A., PH.D., Associate Professor of Histology and Embryology, University of Virginia. Pp. 613; 473 figures and 31 plates. New York: D. Appleton & Co., 1926.

THIS volume is the outcome of eighteen years of experience in teaching embryology to medical students, and gives a well-balanced account of the normal developmental processes in mammals, with special reference to the human organism. Where gaps exist in our knowledge of human development, as during the first three weeks, material derived from comparative embryological sources is utilized. Frequent references are made to conditions of abnormal development, and their explanations discussed. Special chap-

ters are devoted to sex determination, the recapitulation theory, teratology and eugenics. At the end brief laboratory exercises are given on spermiogenesis, fertilization and cleavage, as well as on early stages of pig and chick embryos, with illustrative drawings. The book is written in an interesting style, and contains much well-selected data, indicating a thorough survey of modern literature. The illustrations are numerous and derived from a great variety of sources. This account of the important phases of embryology will be helpful not only to the student, but also to the practitioner who has developmental problems to solve. W. A.

ULTRAVIOLET RAYS IN GENERAL PRACTICE. By W. ANNANDALE TROUP, M.C., M.B., CH.B. (ST. ANDREWS). Pp. 59; 12 illustrations. London: H. K. Lewis & Co., Ltd., 1926. Price, 4/6 net.

OBSERVATIONS covering eighteen months with a new therapeutic agent in a limited number of cases under the eye of one observer seems too restricted in its scope to warrant the passing of final judgment upon it.

A preliminary report might have covered the subject fully.

P. S.

THE NORMAL CHILD AND HOW TO KEEP IT NORMAL IN MIND AND MORALS. By B. SACHS, M.D., Neurologist, Mt. Sinai Hospital, New York. Pp. 105. New York: Paul B. Hoeber, Inc., 1926. Price, \$1.50.

THIS is a very readable little book on a very vital topic, written by one of mature judgment. While the author does not decry all the newer ideas brought out in the study of child guidance, he does not accept Freud's teachings and makes a plea throughout the entire book for the application of rules of common sense. It is a book that can be placed in the hands of parents; it can be understood by all.

N. W.

CLINICAL EXAMINATION OF THE NERVOUS SYSTEM. By G. H. MONRAD-KROHN, M.D., Professor of Medicine in the Royal University, Oslo. Third edition. Pp. 201; 52 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, \$2.50.

THE author enters into the spirit of examinations and gives us a work unhampered by impertinent matter. Psychoanalysis is

included but not in the Freudian sense of "digging up one or more supposed suppressed 'complexes'." The new material embraces pharmacological tests of the vegetative nervous system, pilomotor and postural reflexes, cisterna magna puncture and the employment lipiodol injections in Roentgen ray studies. Except for the absence of fibrositis and its relation to neuralgia and neuritis, the book defies criticism.

N. Y.

PRINCIPLES AND PRACTICE OF ORAL SURGERY. By S. L. SILVERMAN, D.D.S., F.A.C.D., Clinical Professor of Oral Surgery, Atlanta-Southern Dental College; Associate Professor of Surgery (Oral), Emory University, School of Medicine; formerly Special Lecturer on Oral Surgery, Columbia University, New York City; Oral Surgeon to the City (Grady) Hospital, Scottish Rite, Piedmont and St. Joseph Hospitals; Consulting Oral Surgeon to U. S. Veterans' Hospital, Atlanta, Ga. Pp. 326; 280 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, \$6.00.

THE title of this new book is misleading. One expecting a more comprehensive work is disappointed. The principles of surgery are scarcely touched upon, while the simple procedure of Hilton's method of opening an abscess is illustrated by several life-sized photographs.

Bickham's *Surgery* is the source of many artistically correct operations on the tongue—operations seldom or never used at the present time.

Roentgen ray, radium and electrothermic methods are given scant courtesy.

In outlining treatment of fractures of the jaw wiring of the teeth alone is sanctioned. Gilmore's work is ignored. Intermaxillary and interdental splints are mentioned only to condemn them.

The chapter on speech training was written by Dr. G. Hudson Makuen, who died in Philadelphia five years ago.

The book adds little to the literature on oral surgery.

M. D.

HYGIEIA, OR DISEASE AND EVOLUTION. By BURTON PETER THOM, M.D. Pp. 107. New York: E. P. Dutton & Co., 1926.

UNRELATED to that journal which so well popularizes modern medicine for the laity, this latest namesake of the goddess of health discusses in the "Today and Tomorrow Series" the nature of disease "as an element in biologic evolution and its sociologic effect on the progress of civilization." Illustrative incursions into paleopathology, bacteriology, immunity cancer research and so forth pave the way to the conclusion that "*per ardua (or is it aspera?) ad astra*," the golden age is yet to come.

E. K.

PNEUMOCONIOSIS (SILICOSIS). By HENRY K. PANCOAST, M.D., Professor of Roentgenology, University of Pennsylvania; Roentgenologist to the University Hospital, Philadelphia; Consulting Physiologist to the United States Bureau of Mines and so forth; and EUGENE P. PENDERGRASS, M.D., Associate in Roentgenology, University of Pennsylvania; Assistant Roentgenologist to the University Hospital, Philadelphia. Pp. 186; 23 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, \$4.00.

THE word-rich, the thought-poor group of medical writers does not number among its members the authors of this splendid monograph. It is short, complete and concise. The flow of thought is rapid and clearly expressed. Words are not wasted.

Special mention must be made of the chapter on pathology. Having once grasped the mechanics of the processes resulting in pneumoconiosis (silicosis), which is well presented, the interpretation of the roentgenographic changes is facilitated and rendered rational.

The Roentgen ray film reproductions are well chosen and cover the subject thoroughly. The three stages are clearly shown and differentiated, while considerable attention is given to "coincident tuberculosis." The importance of this infection to the individual, his associates and employers, as evidenced by the Workmen's Compensation Laws of Great Britain and South Africa, is carefully considered.

One of the most excellent parts of this monograph is the résumé accompanying each film reproduction. It contains an abstract of the case history and the roentgenographic interpretation. For the student this is invaluable, while others will find it a storehouse of information.

P. S.

AN INTRODUCTION TO THE PRACTICE OF PREVENTIVE MEDICINE. By J. G. FITZGERALD, M.D., LL.D., F.R.S.C., assisted by PETER GILLESPIE, M.Sc., C.E., M.E.I.C., and H. M. LANCASTER, B.A., Sc.D. Second edition. Pp. 792; 130 illustrations. St. Louis: The C. V. Mosby Company, 1926. Price, \$7.50.

THERE has been a general revision of the different sections of the book. Much of the material contained in appendices in the first edition has been incorporated in the appropriate chapters.

The advances in knowledge of the communicable diseases, especially in scarlet fever, have been incorporated. The use of charts helps to emphasize important phases of the subject. Each chapter has appended an extended list of references which enable the student to consult other important texts.

The book is designed especially to meet the needs of students pursuing a practical course in preventive medicine.

D. B.

THE LIFE AND TIME OF ADOLF KUSSMAUL. By THEODORE H. BAST, PH.D., Associate Professor of Anatomy, University of Wisconsin Medical School. Pp. 131; 5 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, \$1.50.

A SYMPATHETIC account of a great clinician, with an illuminating picture of German medicine in midnineteenth century, reprinted from the *Annals of Medical History*. The important connections between Kussmaul (an etymologic descendant of Oribasius) and the ophthalmoscope, esophagoscope, stomach tube, periarteritis nodosa, Kussmaul's dyspnea and the pulsus paradoxus are sketched, and a summary of his literary works given in the form of an appendix.

E. K.

THE MEANING OF DISEASE. By WILLIAM A. WHITE, M.D. Pp. 220. Baltimore: The Williams & Wilkins Company, 1926. Price, \$3.00.

ON the basis that medical thought has too long been chiefly analytical, the author feels that the time is ripe to formulate a theory of disease by synthetic philosophizing. He considers disease as the conflict in the animal organism between the action of various harmful agents and the effort of the organism to return to a normal condition. Believing in the essential creativeness of thought, he does not "hesitate to use speculation, hypothesis and theory in his synthesis;" but to those more accustomed to advance by observation and experimentation, as well as by thought, the book will present a deal of hard reading, without, in the reviewer's opinion, a corresponding advance in our knowledge of the problem of disease.

E. K.

DISEASES OF WOMEN. By HARRY S. CROSSEN, M.D., F.A.C.S., Professor of Clinical Gynecology, Washington University Medical School. Sixth edition. Pp. 1005; 934 illustrations. St. Louis: The C. V. Mosby Company, 1926. Price, \$11.00.

WHEN the present reviewer had the privilege of reviewing a previous edition of this work, he stated that he considered it one of the best textbooks in its field. After reading the present edition he has no reason to change that opinion. As evidence of how this book has been brought up-to-date, may be mentioned the inclusion of work on the use of iodinated oil in gynecologic diagnosis, which only appeared in current medical literature four months previously. This book will be of real value in the library of the student or practitioner.

F. B.

PRACTICAL SURGERY OF THE JOSEPH PRICE HOSPITAL. By JAMES WILLIAM KENNEDY, M.D., F.A.C.S., Surgeon to the Joseph Price Hospital, Philadelphia. Pp. 861; 129 illustrations. Philadelphia: F. A. Davis Company, 1926. Price, \$10.00.

To those who remember the unique character of the late Joseph Price, this book will be welcomed as a memorial, particularly the introductory biographic sketch and the short section of Price's epigrammatic sayings which ends the volume. So much for its sentimental value. As to its value as a scientific contribution, this is a dangerous book to place in the hands of students or young practitioners, but will be read by experienced surgeons with interest, though in many places not with approval. It is poorly written and shows lack of careful revision with regard to spelling and grammatical construction.

F. B.

CAVERNOUS SINUS THROMBOPHLEBITIS AND ALLIED SEPTIC AND TRAUMATIC LESIONS OF THE BASAL VENOUS SINUSES, A CLINICAL STUDY OF BLOOD STREAM INFECTION. By WELLS P. EAGLETON, M.D. New York: The Macmillan Company, 1926.

THIS is a valuable monograph, based on the author's personal experience with one of the most difficult problems in intracranial surgery. The author has for many years been one of the foremost Americans working in this field, and this book is the expression of his views with a detailed report of the cases and so forth on which they are based. He believes that by far the larger number of cases of brain abscess and meningitis are caused by the infective process travelling by way of an infective retrograde thrombophlebitis, and not by direct extension of the suppuration. The latter has become progressively rarer with the advent of early attack on the primary focus in the mastoid or accessory sinuses. He emphasizes the fact that the only chance for the operative relief of these cases rests on early diagnosis and prompt surgical intervention, followed by vaccine or serum therapy. The diagnosis between a cavernous sinus thrombophlebitis of acute onset, and one of slow onset progressing gradually, is of great importance, as the latter frequently does not present the chemosis of the orbital tissues and other classical symptoms associated with the condition. The points in the diagnosis between thrombophlebitis, brain abscess and meningitis are well brought out, and frequent blood cultures are advised to detect or eliminate blood stream infection. Attention is directed to the phenomenon, so often seen of apparent wellbeing in a patient with blood stream infection. The author regards a positive blood culture as absolutely diagnostic of phlebitis of a large sinus. The book is an important contribution on a subject of the utmost interest to otologic surgery.

F. P.

A PRIMER FOR DIABETIC PATIENTS. By RUSSELL M. WILDER, M.D., Section on Nutrition, Division of Medicine, Mayo Clinic. Third edition, reset. Pp. 134; 4 illustrations. Philadelphia and London: W. B. Saunders Company, 1927. Price, \$1.50.

THIS little manual will no doubt be found a useful adjunct to the physician's instructions to his diabetic patients. One is tempted, however, to criticise the instructions for insulin administration; doses of equal size before each meal being recommended, instead of giving proportionately more before breakfast, when the blood sugar is highest. The recommendation of a proprietary brand of digitalis to be given intramuscularly in treating acidosis and coma might also be criticized.

J. A.

BOOKS RECEIVED.

Diseases of the Digestive Organs. By CHARLES D. AARON, Sc.D. M.D., F.A.C.P. Fourth edition. Pp. 927; 257 illustrations. Philadelphia: Lea & Febiger, 1927. Price, \$11.00. (To be reviewed later.)

History of Cardiology. By LOUIS FAUGERES BISHOP, M.A., M.D., Sc.D., F.A.C.P. Pp. 71; 12 illustrations. New York: Medical Life Press, 1927. Price, \$5.00. (To be reviewed later.)

Immunity in Syphilis. By ALAN CHESNEY, M.D. Pp. 85. Baltimore: Williams & Wilkins Company, 1927. Price, \$2.50. (To be reviewed later.)

The Elements of General Zoölogy. By WILLIAM J. DAKIN, D.Sc. Pp. 496; 252 illustrations. New York: Oxford University Press, American Branch, 1927. Price, \$4.00. An "elementary textbook on animal biology" in which mammals play but a small part.

Trabajos y Publicaciones de la Clinica del Prof. Pedro Escudero. Pp. 426; 6 illustrations. Buenos Aires, El Ateneo, 1925. An interesting and useful publication even to those but slightly acquainted with Spanish.

The Harrey Lectures 1925-1926. Delivered by F. R. NAGER, M.D., JOHN H. WINTHROP, M.D., WARREN H. LEWIS, M.D., EDWIN B. WILSON, M.D., KNUD FABER, M.D., B. BROUWER, M.D., and J. B. COLLIP. Pp. 250; illustrated. Baltimore: Williams & Wilkins Company, 1927. Price, \$4.00.

Examination of Children by Clinical and Laboratory Methods. By ABRAHAM LEVINSON, B.S., M.D. Second edition. Pp. 192; 85 illustrations. St. Louis: C. V. Mosby Company, 1927. Price, \$3.50. (To be reviewed later.)

- Mother and Unborn Child.* By SAMUEL RAYNOR MEAKER. Pp. 209; 22 illustrations. Baltimore: Williams & Wilkins Company, 1927. Price, \$2.50. (To be reviewed later.)
- The Psycho-pathology of Tuberculosis.* By D. G. MACLEOD MUNRO, M.D., C.M., M.R.C.P. (EDIN.). Pp. 92. New York: Oxford University Press, American Branch, 1927. Price, \$1.75. (To be reviewed later.)
- A Practical Treatise on Diseases of the Skin.* By OLIVER S. ORMSBY, M.D. Third edition. Pp. 1262, 524 illustrations. Philadelphia: Lea & Febiger, 1927. Price, \$11.00. (To be reviewed later.)
- Thought and the Brain.* By HENRI PIÉRON. Translated by C. K. OGDEN. Pp. 262; 20 illustrations. New York: Harcourt, Brace & Co., 1927. Price, \$4.00. (To be reviewed later.)
- Elements of Hygiene and Public Health.* By CHARLES PORTER, M.D., B.Sc., M.R.C.P. (EDIN.). Second edition. Pp. 425; 98 illustrations. New York: Oxford University Press, American Branch, 1927. Price, \$4.50. A sound useful book for the undergraduate. Not to be confused with larger works of greater merit.
- Management of the Sick Infant.* By LANGLEY PORTER, B.S., M.D., M.R.C.S. (ENG.) and WILLIAM E. CARTER, M.D. Pp. 726; 73 illustrations. St. Louis: C. V. Mosby Company, 1927. Price, \$8.50. (To be reviewed later.)
- The Tired Child.* By MAX SEHAM, M.D., and GRETE SEHAM, PH.D. Pp. 342; 20 illustrations. Philadelphia: J. B. Lippincott Company, 1927. A discussion of the "various conditions acting . . . to produce chronic fatigue in infancy and childhood" and how to prevent or remove their evil consequences.
- The Fifth Avenue Hospital Clinics.* Pp. 336; 67 illustrations. New York: Paul B. Hoeber, Inc., 1927. Price, \$5.00.
- Saving Eyesight after Mid-life.* By JOHN HERBERT WAITE, M.D., S.M. Pp. 48; 6 illustrations. Cambridge: Harvard University Press, 1927. Price, \$1.00. (To be reviewed later.)
- Symbiontism and the Origin of Species.* By IVAN E. WALLIN, Sc.D. Pp. 171. Baltimore: Williams & Wilkins Company, 1927. An exposition of the unqualified view that mitochondria are microorganisms symbiotically united to the cell with speculations on the changes that such a theory imposes on heredity, evolution, cell structure, etc.
- Medical Science for Everyday Use.* By WARREN SHIELDS, A.B., M.D. Pp. 178. Philadelphia: Lea & Febiger, 1927. Price, \$2.00. (To be reviewed later.)

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Mineral Salt Content of the Blood in Disease.—A. S. BLUMGARTEN and GEORGE ROHDENBURG (*Arch. Int. Med.*, 1927, 39, 372) report upon the mineral salt content in the blood in disease and have brought out some interesting figures as a result of their studies. Sodium makes up 40 to 55 per cent of the mineral salt content of the blood; potassium 35 to 45 per cent; calcium 2 to 3 per cent and magnesium 1 to 1.5 per cent. The total salts are from 250 to 300 mg. per 100 cc. Sodium and potassium have a certain reciprocal relationship whereby when one is increased, the other diminishes. In cancer, leukemia and purpura hemorrhagica there is associated quite a marked disturbance of the circulating mineral salts. In cancer the magnesium was very low, as was the calcium. In leukemia and purpura hemorrhagica the potassium content was low. Chronic nephritis showed a high sodium and low calcium. High magnesium figures were found in arteriosclerosis and in old individuals.

An Experimental Investigation as to a Possible Etiologic Relationship of Monilia Psilosis to Pernicious Anemia. A Control of E. J. Wood's Work.—One of the theories of the causation of sprue has been the growth within the intestinal tract of *Monilia psilosis*. This theory has been advanced and upheld largely by Ashford and has not been concurred in by many of the workers in tropical sprue in this country and Europe. Sprue is a disease which is closely akin to pernicious anemia in many of its manifestations, more particularly in the character of the blood picture. Acting on the hypothesis that sprue and pernicious anemia may be etiologically identical and that sprue is caused by a monilia, E. J. Wood recently published in the *AMERICAN JOURNAL OF MEDICAL SCIENCES* an interesting and thorough, clinical and experimental study of the two conditions. It is his belief, as a result of his studies, that the yeasts have hemolytic action on the blood and are responsible for the anemia that is recognized as pernicious anemia and which is

found in sprue. A. S. WARTHIN (*Ann. Clin. Med.*, 1927, 5, 808) has attempted to repeat Wood's experiments and was completely unable to do so. The author was not able to develop an anemia in any of his experimental animals nor was he able to show that any pathologic changes were produced in animals by any of the three strains of *Monilia psilosis* that he used. It is interesting to note the complete variation in the results of the two studies. It might be suggested that strains of monilia grown from the feces of cases of pernicious anemia might have a totally different biologic reaction when implanted in experimental animals than the strains which have been passed down in laboratories by repeated transference of culture. Variations in the virulency of bacteria as a result of repeated subcultures is well known. Perhaps in this fact lies the explanation for the action of these yeasts that have just been studied.

Sickle Cell Anemia: Report of a Case Greatly Improved by Splenectomy. Experimental Study of Sickle Cell Formation.—It is an interesting observation that in any of the sciences when something is once pointed out, a large number of similar instances are found to occur. Such is the case with sickle cell anemia. Originally thought to be a condition which was extremely rare, it is now found that this disease is quite frequent, some estimating that the peculiar sickle cell red cell may be found in from 1 to 2 per cent of the negro population. E. V. HAHN and E. B. GILLESPIE (*Arch. Int. Med.*, 1927, 39, 233) report a case of sickle cell anemia and, furthermore, report a series of experiments which they undertook to determine the cause and pathogenesis of the condition. They found that in individuals with a sickle cell trait, the red corpuscles are transformed into sickle cells *in vitro* as a result of asphyxiation and that the sickle distortion is a reversible phenomenon. Oxygen and carbon monoxide will cause the cells to come back to normal shape. They advance the hypothesis that the sickle form is stable when hemoglobin is dissociated, and that the discoid form is stable when the hemoglobin is combined. They believe that the only specific cause for active sickle cell anemia is the hereditary anomaly of the red cells. A patient with this type of anemia is greatly improved by splenectomy.

10,300,000 Vaccinations for Smallpox without One Single Reported Case of Syphilis.—A note has been published by SURGEON GENERALS IRELAND, STITT and CUMMING (*Science*, 1927, 65, 372) which is deserving of wider spread dissemination than it probably will receive from this source of publication. This note has to do with the large number of men who have been vaccinated against smallpox in the United States Army, Navy and Public Health Service, and is written for the purpose of combating false statements that are being circulated among the laity in which it is recounted that vaccination often causes syphilis. The very large number of vaccinations that have been performed by the several services of the United States Government without one patient ever developing syphilis as a result of vaccination should do much to ease the mind of the general public and will be a valuable argument for members of the medical profession, who of course are aware that the disease is confined to the human species and that therefore calf vaccines cannot transmit the disease.

SURGERY

UNDER THE CHARGE OF

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Carcinoma of the Mouth: Types and Degrees of Malignancy.—BRODERS (*Am. J. Roent. and Rad. Therap.*, 1927, 17, 90) states that the mouth, like the urinary tract, is lined with a protective covering of epithelium in contradistinction to the gland or secretory epithelium of the gastrointestinal tract. Carcinomas that arise from the regenerative cells of the protective epithelium of the mouth are far more numerous than those that arise from the regenerative cells of the gland epithelium, which naturally incites more interest in the former group. From a practical standpoint there are, therefore, two general groups—epitheliomas from the protective epithelium and adenocarcinomas from the gland epithelium. The first group (epitheliomas), depending on the manner of cell differentiation, is divided into squamous-cell epithelioma, basal-cell epithelioma, melanotic epithelioma, nonmelanotic melanoeptithelioma, adamantine epithelioma or adamantinoma and mixed epithelioma. The second group (adenocarcinoma), depending on the manner of cell differentiation, is divided into colloid or mucoid carcinoma, pseudomucinous carcinoma and so forth. The descriptive terms complicate instead of simplify the terminology by converting descriptive terms into entities, as a number of these terms may be applicable to one type of carcinoma. The so-called mixed tumor is nothing more than an adenocarcinoma that has cartilage and sometimes bone around its cells for protection of the host. As regards the cause of carcinoma, all writers lay great stress on irritation. The author believes that irritation plays the lesser and heredity the greater part in the cause of spontaneous cancer. One cannot ignore the great influence of heredity in the face of the facts elicited in the epoch-making work of Maud Slye. The author appends an interesting method of grading malignancy in this excellent classification.

Large Ureteral Calculi.—BRIGGS (*Urol. and Cutan. Rev.*, 1926, 30, 702) says that the rapid growth of stones is not especially remarkable, since experience teaches us that oftentimes stones in the ureter, as well as in the bladder, increases rapidly in size. Large ureteral calculi sometimes cause no symptoms for a long time and even if there are symptoms they do not necessarily suggest the urinary tract. The author states that it might be well to emphasize the importance of suspecting diverticulum of the bladder in the any patient under fifty years of age, who in the absence of stricture, stone or rectal enlargement of the prostate suffers from symptoms of prostatism.

Bronchography.—SINGER (*Arch. Surg.*, 1927, 14, 167) writes that the value of bronchography lies in the definite mapping out of lung structure, either normal, or altered by pathologic conditions. It requires considerable experience to be able to interpret these shadows, especially with so dense and so opaque a substance (iodized oil, 40 per cent). True interpretation will be made in conjunction with the physical signs and history. Many dense shadows in the roentgenogram may be tumor masses, collapsed lung tissue or cavities filled with secretion. The opacity of the iodized oil (40 per cent) when introduced into the lungs of these patients will often give startling pictures of pathologic conditions that were not suspected. This method should not be used in any case where simpler methods can be used. It does, however, show excellently the bronchial tree with abnormalities present, and when properly used it is harmless. The author describes various methods for patients of different ages. The author gives five methods of technique. Approximately from 20 to 40 cc. of the oil must be used to produce suitable roentgenograms. The intratracheal method is described here. Beforehand the patient is given $\frac{1}{4}$ gr. of morphin and the larynx is then thoroughly anesthetized with a 20 per cent solution of cocain. One must wait five minutes or more until the cough reflex is entirely abolished. The oil is then introduced intratracheally through a tracheal catheter. The oil is slightly warmed before being forced into the catheter.

Thyroiditis Accompanied by Hyperthyroidism.—BRENIZER (*Ann. Surg.*, 1927, 85, 339) states that experimental evidence shows that the thyroid can become infected by direct injections of small masses of tubercle bacilli, just as other organs, the spleen, kidneys and testicles, can become infected. The susceptibility of the thyroid for tuberculous infection is less than in the other named organs. This evidence would go to prove the possibility of a bacterial invasion of the thyroid by way of the blood route. The author's reported cases strongly indicate direct bacterial invasion by contact and possibly by the lymphatic route. Thyroiditis is rare however; probably 0.5 to 1 per cent of all operative material and 0.25 to 0.5 per cent of all observed clinical cases. The two most frequently proven types of inflammation are tuberculous and woody thyroiditis. Syphilitic thyroiditis certainly occurs. Nonspecific thyroiditis has shown its bacterial cause in some suppurating cases. Hyperthyroidism may accompany any type of thyroiditis at any stage—usually the subacute stage. The relation in tuberculous thyroiditis is striking. Most cases of nonspecific and woody thyroiditis finally become hypothyroid whether operated upon or not. Cases of tuberculous thyroiditis operated upon have given the best functional lasting results. Syphilitic thyroiditis has been relieved with appropriate treatment. Therefore, the more slowly progressive and destructive type of inflammation is more apt to be accompanied pathologically by hyperplasia and signs of hyperthyroidism and is more apt to give better functional results after operation. The usual amount of thyroid should not be removed even in tuberculous thyroiditis, for at least 1 case out of 13 has resulted in myxedema.

PEDIATRICS

UNDER THE CHARGE OF

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The Absorption of Calcium from the Intestinal Tract of Human Subjects: the Influence of Foods.—ROE and KAHN (*J. Am. Med. Assn.*, 1927, 88, 980) feel that their experiments are not to be interpreted as indicating that the calcium of foods is not readily absorbed. Their studies were concerned with the absorption of calcium when large quantities of calcium salts were ingested with and without foods. It had been shown previously by others that the average calcium requirement of an adult is 0.45 gm. a day. This amount is absorbed over a period of twenty-four hours and absorption is accompanied by excretion in like degree, since, in the adult, there is little if any calcium storage. Under normal dietary conditions the serum calcium concentration at any time during the absorptive period is not appreciably changed, and, therefore, the estimation of the serum calcium is not the method that can be applied to the study of calcium absorption from the alimentary tract from foods containing the usual amount of calcium. Their belief is that the best therapeutic results will be obtained by the oral administration of calcium lactate in 5 gm. doses in aqueous solution at least a half hour before breakfast and at bedtime at least three hours after the last food was taken. Their experiments showed that intravenous injection of calcium salts is not justified since proper oral administration produces a prolonged serum calcium elevation and does not incur the dangers of the intravenous technique. There is a prevailing opinion concerning the etiology of rickets that there is a diminished absorption of calcium from the alimentary tract even though calcium is present in the diet in ample amount. The feeding of calcium as a prophylactic or therapeutic measure has often failed to prevent or cure rickets. It is possible that these experiments offer an explanation of such results. They believe that therapeutic results will be more uniform when calcium is properly administered and that deductions as to the therapeutic value of calcium salts should be delayed until a sufficient amount of work on various diseases under the best absorptive conditions has been accumulated.

Studies of Citrated Blood: Behavior of Platelets.—GICHNER (*J. Am. Med. Assn.*, 1927, 88, 893) made this study to determine the value of citrated blood in transfusion. Pharmacologic studies of sodium citrate show that this substance is nontoxic in a much larger dose than that used in transfusion. This removal from the recipient's body probably leaves the platelets capable of performing their normal rôle in coagulation. Long clinical experience with sodium citrate as an anticoagulant in transfusion has resulted in a fairly general feeling that blood so

treated is utilized by the recipient just as the blood to which no anti-coagulant has been added. The platelets show a definite behavior in the clotting of blood *in vitro*. Sodium citrate in sufficient concentration completely inhibits their activity. If a sufficient concentration of calcium is added or the concentration of citrate is sufficiently lessened the platelets behave as in unmodified blood. Platelet-free mammalian plasma will not spontaneously coagulate under circumstances that cause coagulation of platelet-rich plasma. He was unable to show that the injection of citrated blood causes a diminution of the recipient's platelets. He found that disodium citrate does not cause changes in blood which would contraindicate its use in any case in which therapeutic transfusion of blood is indicated.

Helminthic Therapy.—FERNAN-MUNEZ (*J. Am. Med. Assn.*, 1927, 88, 903) states that as *Trichocephalus dispar* and *Oxyuris vermicularis* tend to localize in the appendix and cecum, oral treatment often fails to reach them. Carbon tetrachloride is not efficacious against *Trichocephalus* or *Oxyuris*, although it is fairly useful against the strongyloides family. "Leche de ligueron" by mouth is efficacious against *Trichocephalus dispar*. Oil of chenopodium is the most satisfactory of the common vermifuges against *Trichocephalæ* and *Oxyuris*. Oil of chenopodium by mouth administered in a single dose of 40 minims. followed immediately by an ounce of castor oil is equally efficient, less dangerous and much more convenient for both patient and physician than the more common way used method of divided doses. Oil of chenopodium by intramuscular or intravenous injection is specific against *Trichocephalus* and *Oxyuris*, which are the two most difficult nematodes to eliminate. Arsphenamines given intravenously will often expel intestinal nematodes, but their use as vermifuges is extremely limited. Extracts of eggs of *Trichocephalus* injected into dogs at three-day intervals for one month apparently conferred an immunity against *Trichocephalous* reinfestation for periods varying from seven to twelve months.

Classification of Pulmonary Tuberculosis in Children.—RIESMAN (*Arch. Ped.*, 1927, 44, 165) says that contact infection is of preëminent importance in the spread of tuberculosis in children. It is very important to investigate the history of the grandparents aunts, uncles and even of non-relatives, such as maids and other contacts. It is necessary that all contacts have the tuberculin test to determine the presence or absence of a focus and that all those giving a positive tuberculin test should have a Roentgen ray of the chest to determine the extent of the focus. The diagnosis of the disease is extremely difficult because so few physical signs can be elicited. Roentgen ray has often revealed the presence of considerable pathology where little was suspected from the evidence of physical examination. The classification is dependent upon the three-fold essential to the diagnosis of pulmonary tuberculosis in children. (1) History of contact; (2) a positive tuberculin test; (3) the presence of enlarged tracheobronchial glands as shown by Roentgen ray. The groups into which he divides the disease are: (1) Children who give a definite history of contact, but with a negative tuberculin test; (2) children with a definite history of contact and positive tuber-

culin test, but with no definite evidence of disease nor any appreciable enlargement of the tracheobronchial glands; (3) incipient tuberculosis of childhood in those giving a definite history of contact, a positive tuberculin test and slight enlargement of the tracheobronchial glands as shown by Roentgen ray; (4) massive enlargement of the tracheobronchial glands extending above the root branches and encroaching upon the central lung field and pushing toward the interlobar septum with nodulation, fibrosis and calcification and a positive tuberculin test; (5) the adult type parenchymal infiltration and breaking down of the lung tissue with tendency toward cavity formation and with definite physical signs superimposed upon the juvenile type.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Generalized Telangiectasia.—BECKER (*Arch. Dermat. and Syph.*, 1926, 14, 387) reviewed the literature, collecting 129 cases of generalized telangiectasia which did not include any of the hereditary type and added 7 additional cases which he had thoroughly studied. They are classified in three groups: (1) Generalized telangiectasia; (2) nonhereditary and nonfamilial telangiectasia with involvement of the mucous membranes, and (3) livedo racemosa. Telangiectasia is limited in its meaning to acquired dilatation of the smaller vessels usually visible to the naked eye, being essentially venous terminations of capillaries and venules, sometimes only visible with a loupe. Generalized telangiectasia is differentiated clinically from various dermatoses by the relative permanence of the lesions and by the absence of an appreciable degree of atrophy, purpura, depigmentation and follicular involvement. The lesions in many of the syphilitic cases have consisted of sharply circumscribed macules. Livedo racemosa has a characteristic appearance. Various combinations of macules, papules, puncta, diffuse erythema and other lesions apparently may have the same etiologic background and many factors produce identical pictures, so that gross morphologic classification is not of great value. There is a multiplicity of causative conditions, and it may be this bombardment of the vasomotor mechanism which accounts for the picture. Examination of detailed reports of 68 cases of generalized telangiectasia and 4 of his own cases prompted the author to support Lanceplaines's three etiologic theories—neurogenous, mechanical and toxic—to account for all these

types of cases. The essential histopathologic observations in 3 cases were dilatation and proliferation of capillaries in the corium, usually most evident in the subpapillary zone. When a mechanical factor predominates, endarteritis and periarteritis will be present. In the list of presumably causal agents, syphilis is foremost: Fournier included peripheral vascular dilatation as a stigma of congenital syphilis. One case of the author's was suggestive of congenital syphilis but the most evident causative agents were prolonged pyogenic infection in two and neurogenic factors in the other two. Capillary microscopic examination showed vessels to be definitely dilated in these four. In the second type, (nonhereditary and nonfamilial) 9 cases were found described in the literature and 1 of the author's came in this group, but was probably an example of indirect inheritance. The only distinguished feature of these nonfamilial cases is the tendency to anemia because of repeated attacks of epistaxis. Livedo racemosa is a passive, and stasis hyperemia, consisting essentially of bluish-red, tree-shaped or netlike, usually slightly elevated lesions from 1 to 2 cm. broad. In the 55 cases of this type found in the literature, syphilis and tuberculosis are the main etiologic factors. Ehrman believes the condition always follows cutis marmorata; and he is supported by many other authors. Microscopic studies reveal a considerably higher percentage of inflammatory alteration, than in the general group. This with the predominance of infectious causes lends weight to the belief that the organic changes, viz.: fibroblastic proliferation and thickening of the intima of the dilated vessels, are due to infection. In the author's 2 cases, 1 was distinctly neurogenic in origin and the other due to numerous respiratory infections. A ready reference outline for intensive study is presented, which if followed will practically always elicit the causative factor in every instance.

Nonspecific Stimulation Therapy, Wassermann Reaction and Syphilis Therapy with Living (Malaria) and Dead Lipoid-albumin Compounds.—SCHUMACHER (*Am. J. Syph.*, 1926, 10, 432) believes that treatment with lipoproteins (lipoid-albumin compounds) is specific therapy in a biochemical sense, possessing definite spirillicidal properties. Administration of lipoproteins leads to the production in the system of lipoproteolytic ferments, the presence of which Schumacher was able to demonstrate in previous experiments with yeast (using a yeast-lipoid acid and basic yeast albumin). These ferments not only attack and destroy kindred lipoid-albumin compounds but also attack the lipoprotein of the *Spirochæta pallida*. Milk contains ample quantities of lipoid-albumin compounds; such therapy cannot be now considered nonspecific stimulation therapy (even if so in a bacteriologic sense). Development of lipolytic ferments is not always accompanied by a concomitant positive Wassermann reaction while the latter always turns positive after a preliminary treatment with lipoid-albumin compounds. As the Wassermann reaction may be considered a nonspecific biologic symptom of syphilis, the above phenomenon suggests that it is the result of a systemic defensive reaction. The presence of spirochetes, that is, the presence of living lipoid-albumin compounds, does not cause a production of lipoproteolytic ferments. This is proved by the fact that in the newborn the system is frequently flooded with spirochetes,

while the Wassermann reaction is still found to be negative and even Wassermann himself had corresponding negative findings with the injection of pure cultures of spirochetes. Only the development of dead tissue lipoid-albumin compounds, as a result of the activity of the spirochetes, initiates the production of lipoproteolytic ferments. As to the mode of action of various antisyphilitic agents, arsphenamin exerts a direct action upon the spirochetes. The effect of arsphenamin in animal experimentation is known to be increased if it is administered simultaneously with lipoid-albumins. Mercury and bismuth act essentially indirectly, increasing cell activity which causes an increased production of lipoproteolytic spirillicide ferments which then attack the spirochetes with more intensity than the cells could without this metallic stimulation. The author believes mercury to be the more efficient. As the spirochetes gradually succumb there is further production of autogenous tissue lipoid-albumin compounds. As the activity of the spirochetes in the diseased tissue ceases, the Wassermann reaction becomes negative. The mode of action of iodine still lacks a satisfactory explanation. Malarial therapy is effective because extensive destruction of red blood corpuscles results in the development of autogenous lipoid-albumin compounds similar to those which occur following syphilitic infection of a tissue. The spirochetes in the brain and cord cannot be influenced by arsphenamin as the arsphenamin base is previously bound by the central nervous system, which is rich in lipoproteins. Mercury or bismuth have no worth-while effect in central nervous system degeneration owing to a lack of tissue reaction. An attempt to achieve the same favorable therapeutic results as with malaria infection, by repeated injection of dead lipoid-albumin compounds, seems desirable. In view of the present knowledge of the spirillicidal effect of lipoproteolytic ferments, Schumacher insists that in the future, the earliest possible arsphenamin treatment should be followed by mercury in combination with a suitable lipoid-albumin therapy. This will secure indirectly, *via* the body cells, the devitalization of those spirochetes which escaped the salvarsan base.

OBSTETRICS

UNDER THE CHARGE OF

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The Incidence of Dental Caries in Pregnant Women.—The prenatal care of the obstetrical patient has for many years been attracting wide-

spread attention, and dental caries in the pregnant woman has been a very important factor; only pregnancy is considered a causative factor by ZISKIN (*Am. J. Obst. and Gynec.*, 1926, 12, 710). He covers a large number of cases and gives 25 per cent as number of pregnant cases seen from 1922 to 1925. The age of the patient averages between fifteen and forty-five years and for convenience were divided into six age divisions. The findings were given in tables and diagrams. Table I shows the distribution of cases according to the various ages, and shows the peak of this curve is at the age of twenty-one years. Table II shows a rise of carious teeth and general tendency for the occasion of caries with the increase of age. There is also a general tendency in Table III to the increase of caries with the rise in age. The final analysis given in Table V of the general hospital group and pregnant cases shows that the incidence of caries and missing teeth was actually higher in the hospital group than in the pregnant group but that there is undoubtedly an important factor in pregnancy in relation to the dental manifestation or caries and disease of the teeth.

Suppression of Urine in Connection with Pregnancy.—HIRST (*Am. J. Obst. and Gynec.*, 1926, 12, 673) deals with the types of anuria met with during pregnancy and the puerperal state. Anuria due to kidney degeneration (idiopathic anuria), suppression due to urinary calculus and last ureteral edema. The first type usually accompanies the late gestational toxemias with or without accompanying nephritis. Anuria with these instances is not always accompanied by complete suppression. Second, chemical poisoning, and third, degenerative nephritis. Since the introduction of mercurochrome intravenously, attention has been directed to the possibility of an accompanying suppression. Third, degenerative kidney changes unquestionably due to the metabolic poisoning produce the suppression. The second series of suppression is attributed to renal calculus and its associated edema. The third type is represented with cases of eclampsia, all associated with hydronephrosis with mild or severe ureteral dilatation and edema. The average urinary output following the normal delivery is given as from 29 ounces the first day, increasing daily, until the fifth day, at which time the urinary output rises to 36 ounces or more, and it is pointed out the importance of keeping accurate record of the urinary output, regardless of the intake of fluid until lactation has become definitely established.

A Case of Placenta Accreta.—FORSTER (*Canadian Med. Assn. J.*, 1927, 17, 204) shows the rarity of this complication of pregnancy. Polak has estimated its instance to be about 1 case in 6000. This case occurred in the Montreal Maternity Hospital, over a period of six years, covering 8000 deliveries. In the normal placenta the decidua is everywhere interposed between the villi and the uterine musculature. Its existence in this relation is of the greatest value, as it makes possible the separation of the placenta from the maternal structures. The article and case report emphasizes the fact that when the placenta fails to deliver in the third stage of labor two conditions may exist—one where the placenta is retained in the birth canal, at which time there will be bleeding and the descent of the cord with the ascent of the

fundus of the uterus well contracted to a higher level in the abdomen. In the presence of a placenta accreta the placenta has not separated from the uterine wall, there would be no bleeding and uterine contractions would still be felt. The placenta accreta is the result of the absence of the decidua at the placental site. Hence the placental villi penetrate the uterine musculature, causing the placenta and uterine wall to become one structure and making separation of the placenta from the uterine wall utterly impossible. The predisposing factors in placenta accreta are obviously those which lead to the destruction of the uterine mucosa, such as repeated or too vigorous curettage, endometritis, submucous fibroid and previous manual removal of the placenta. If any of these etiologic factors be present in a given case one must be prepared to deal with such a complication of the third stage. Finally, if no line of cleavage can be demonstrated the patient, having been given an anesthetic, a hysterectomy is indicated and should be done promptly.

Studies in Sterility in Women.—JOHN OSBORN POLAK (*Surg., Gynec. and Obst.*, 1927, 44, 520) claims it is the purpose in this article to bring forth a collective review of this subject. The author classifies the types of sterility, points out the chief etiological factors, suggests methods of arriving at a correct diagnosis and correlates the present methods of treatment. Sterility is classified into Absolute and Relative. Absolute, in which impregnation is impossible due to defect either in the avenue of transit or the absence or defective organs of reproduction themselves. Relative sterility: when the woman does not conceive under normal conditions during the first year of her married life, possibly fetalism, infantilism and endocrine deficiency. A woman is considered sterile after seventeen months of married life when no contraceptive measures have been employed. Secondary sterility is the result of birth traumatism following child or infections of Neisserian origin. There are five basic requisites to conception and the healthy development of the ovum: (1) Healthy active spermatozoa deposited by coitus in the posterior fornix or on the cervical portio; (2) a perfectly matured ovum; (3) a patent tubouterine tract; (4) a normally developed corpus; (5) normal secretions in both man and woman with biochemical reactions which are compatible. The male must be excluded as a causative factor and developmental defects of the woman determined, such as imperforate hymen, rudimentary vagina, total absence of the genital organs, long conical cervix with pin point os, cervical antelexions, retropositions of the uterus, retroversions of the uterus or infravaginal hypertrophy of the cervix. Congenital anomalies in malformation of the uterus, excessive length and tortuosity of the tubes and hypoplasia of the ovaries and the endocranial characteristics of the individual. Coupled with these in the secondary sterility are the relaxed vaginal outlet, varying degrees of descensus, lacerations of the cervix extending through the external os, retroverted subinvolved uterus. Endocervicitis, acute or chronic, has a far reaching pathology. Associated uterine lesions as intramural and submucous tumors, edema, atrophy and hypertrophy of the endometrium all have their influence on possible conception. The very essential factor to be considered in sterility is the question of ovarian function. Hypoplasia of the ovaries, micro-

cystic formation or thickened tunic will not infrequently prevent conception. The author quotes from Rubin that primary sterility in which contributory causes including those in which the husband might be responsible is of a definite diagnostic value. Primary sterility in which the patient is known to have passed through pelvic infection. Sterility following abscess complicating a puerperium. Sterility in which the patient has had a peritonitis of appendicular origin. One child sterility without history of infection. After the surgical removal of pyosalpinx or hydrosalpinx. Unilateral ectopic pregnancy, the patency of the remaining tube determined. After salpingostomy. Tube ligation, tied or severed tubes following multiple myomectomy when the ostium of the tube has not been determined. Following long standing in which the clinical diagnosis of fibroids or chronic disease of the adnexa. The therapeutic tube insufflation to determine the patency of the tubes. There are many unsolved problems in the study of sterility, that cures are brought about often accidentally but a thorough physical and biochemical study and thorough understanding of the female organs of reproduction are essential in dealing with this social, economic and ethical problem.

GYNECOLOGY

UNDER THE CHARGE OF

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Operation for Lacerated Anal Sphincter.—The procedure for the cure of an extensive laceration of the anal sphincter which has given much satisfaction to SISTRUNK (*Ann. Surg.*, 1927, 85, 185) begins with a curved transverse incision just above the anus or along the vaginocutaneous margin. The levator ani muscle is isolated and sutured over the anterior rectal wall, as in an ordinary perineorrhaphy. The ends of the external sphincter which are often widely separated are isolated and sutured to the levator ani, the ends being brought together as closely as possible without too much tension. If sutured under too much tension, satisfactory healing will not occur, as the tissues will slough and the sutures fail to hold. The ends of the muscle are usually brought close enough to close the anus so that it fits snugly around an index finger introduced into the rectum. The wound is left open and packed with iodoform gauze, as is done in operations for rectal fistula. The gauze is usually held in position by a suture placed through the edges of the skin and loosely tied in such a way that the edges of the skin are left wide open. After seven or eight days it may be removed and a healthy granulating surface usually results which slowly heals. The scar tissue which forms in the healing process unites the edges of the sphincter fairly satisfactorily. If the nerve supply to this muscle is uninjured, the patient usually develops normal control; if it has been

injured, normal control will not be gained but the patient will usually be able to close the external sphincter voluntarily by elevating the levator and through efforts to close the vagina or to lift the rectum upward. Through this voluntary effort patients are usually able to control feces and gas and thereby obtain great mental relief. Sistrunk claims that this operation gives better voluntary control than the ordinary operation in which the sphincter ends are merely sutured together but are not sutured to the levator ani muscle.

The Carbon Monoxid Menace and the Cancer Problem.—Many and devious have been the scientific paths traveled by experimenters and research workers in the solution or attempted solution of their problems. This is perhaps nowhere better exemplified than in the present status of the cancer problem, which is being attacked from innumerable angles. For example, LUDEN (*Canadian Med. Assn. J.*, 1927, 17, 43) who is associated with the cancer research division of the Mayo Clinic has been considering the relationship of the carbon monoxid menace and the cancer problem. Of course, he realizes that it would be absurd to look on carbon monoxid as a so-called cause of cancer. We do know however, that cancer is on the increase and that the contamination of the atmosphere by carbon monoxid is becoming more and more a hazard of urban life. Furthermore, that the relative oxygen deficit caused by inhalation of the deadly gas is capable of upsetting the normal body chemistry, is amply proved by the after-effects, the diversity of which seem explicable only by a *locus minoris resistentiæ* in the victim. The exact chemical disturbance required to promote abnormal cell proliferation has not yet been discovered but the chemical aspects of the cancer problem are no longer deemed the day dreams of deluded enthusiasts.

Roentgen Ray Treatment of Pelvic Tuberculosis.—In a follow-up study of 32 patients with pelvic or abdominal tuberculosis over a period of from two to six years following treatment by the Roentgen ray at the Mayo Clinic, FORD (*Minnesota Medicine*, 1927, 10, 32) states there were definite evidences of improvement in 66 per cent of the cases. The continued well-being of patients suffering from tuberculosis is dependent on many hygienic factors, avoidance of overfatigue and freedom from intercurrent infections. Although Ford is identified with the Section on Roentgen Therapy, he concludes from the statistics of this small group that Roentgen therapy in itself has apparently not increased the percentage of continued cures in these cases over that obtained by other methods. However, Roentgen ray treatment, from its average tendency toward amelioration may well be considered a method worthy of thorough trial in cases of abdominal or pelvic tuberculosis. Speaking of tuberculosis of the female generative organs in the pelvis it has been our experience that very many of these patients remain well for many years after the primary focus of infection in the pelvis has been removed, and it would be well for the reader not to consider the value of Roentgen ray therapy until after the patient has had the chance of eradication of the local disease by an abdominal operation. If the general condition does not improve following such operation, as it generally does unless the case is in the late stage, Roentgen therapy may then be of great aid in bringing about the desired result.

Radium Treatment of Uterine Cancer.—One of the few available reports of the clinical results of radium therapy which have come from Japan in recent years is that of IKEDA (*Zentralblatt f. Gyn.*, 1927, 51, 407) of Saga. His opinion and results are worthy of attention, backed, as they are, by an experience of twelve years in radium therapy. He is so well satisfied with the results obtained by this newer method of treatment that he has completely discarded both the vaginal and the abdominal cancer operations. In the period from 1915 to 1923 he treated 432 cases of cancer of the cervix and 18 cases of cancer of the uterine fundus. Of the 432 cervical cancers which were irradiated, 198 (45.8 per cent) are still alive. He has been impressed with the fact that most of the recurrences occur between the end of the first and the end of the second year, although, of course, some occur as late as eleven years after treatment. There were 2 cases which died from septic peritonitis following irradiation, so that he places the primary mortality of this form of treatment at 0.4 per cent. His technique consists of the application of 100 mg. of radium bromid into the cervical canal and 200 mg. against the portio in the vagina for twenty-four hours. This is repeated in the same or smaller dosage after from one to three weeks. In 4 cases the carcinoma was complicated by a myoma and in these cases the myoma was greatly influenced by the irradiation, the menses ceasing and the tumor decreasing in size. In 7 cases the carcinoma was complicated by a pregnancy. Two of these aborted at two and three months respectively during the course of treatment and later died at home. The other 5 cases were in the latter half of pregnancy and went to term and had normal deliveries of normal children. Three of the women subsequently again became pregnant and were delivered at term but all three died of hemorrhage. On this account as well as on account of the scar tissue which forms in the birth canal following irradiation, Ikeda believes that such patients should always be delivered by Cæsarian section.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Surgical Treatment of Vertigo due to Changes in the Endolymphatic Sac.—Any contribution to our understanding of that most harassing symptom—vertigo—is worthy of note. Having learned that vertigo can be caused by increased pressure in the *saccus endolymphaticus*, PORTMANN (*Presse méd.*, 1926, 34, 1635) reports the recovery of two such patients following opening of the internal ear by a technique which he describes. The increased pressure can be caused by compression of the sac from lesions of the meninges, cerebellum or lateral sinus. In addition to such intracranial complications, local inflammatory processes, usually of a serous nature, in the sac may produce sufficient pressure to cause the phenomenon.

Irradiation of Diseased Tonsils.—SCAL (*Med. J. and Rec.*, 1926, 124, 873) describes a method, which was developed by Muir, of treating tonsillar hypertrophies with removable platinum Radon seeds. By means of an implanter, which the author describes and illustrates, the seeds are introduced into the central area of the tonsil so that radiation is distributed equally. The Radon seed is filtered by 0.3 mm. of platinum, which screens the caustic beta rays and obviates burning, with its consequent necroses and sloughing. At the end of four days, the seeds can be removed by grasping a 2 cm. thread which is attached to them at the time of implantation. The author emphasizes the absence of pain, anesthesia, hospitalization, disability, shock and other systemic reactions as advantages of this method. He says that only one treatment is necessary and concludes "that in the implantation of removable platinum Radon seeds we have at present an adequate substitute for tonsillectomy in those cases where surgery is, for any reason, contraindicated."

Observations on Hearing-Acuity for Bone-transmitted Sound.—Having demonstrated that bone-transmitted sound follows at least part of the pathway to the labyrinth taken by air-transmitted sound, that the acuity for air-transmitted sound is not necessarily a criterion for the bone-sensitivity, or *vice versa*, that in Paracousis willisi the deafened do not really hear better in a noisy place, but rather normal persons do not hear so well, POHLMAN and KRANZ (*Proc. Soc. Exper. Biol. and Med.*, 1927, 24, 456) give further observations on the hearing acuity for bone-transmitted sound in two subjects. After extensive study, using various test conditions, they found that the acoustic fan seemed to be a method available to otologists, in determining the acuity for bone-transmitted speech. The acoustic fan is made of flexible hard rubber, fitted with a string which serves to pull the surface of the fan into a bowed or bent form and maintain it in this position. The fan is held by the handle with the top of the fan bent toward the person and the upper edge held firmly between the teeth. The authors also state that "if the diagnosis in the case reported by SABINE (*Laryngoscope*, 1921, 31, 819) is correct, then the fan may be employed as an aid to the diagnosis of stapedial fixation."

RADIOLOGY

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A Review of Our Present Knowledge of Pneumonoconiosis, Based Upon Roentgenologic Studies, with Notes on the Pathology of the Condition.—In this very complete paper PANCOAST and PENDERGRAAS

(*Am. J. Roent. and Rad. Ther.*, 1925, 14, 381) give particular attention to the pathology and roentgenologic diagnosis. The roentgenographic appearances of the first stage are characterized by an increase of the hilum shadows of the central zone, thickening of trunk shadows of the mid-zone and increased prominence of the linear markings of the peripheral zone. Large tracheo-bronchial lymph nodes are common. Because of the lymph drainage, the outermost basal trunks are not so markedly affected as the more mesial ones. In this stage interference with diaphragmatic movement is not so noticeable. These changes are brought about almost entirely by fibrosis or lymph blockage. In the second stage there is a typical mottling throughout the lungs caused by small fibrotic nodules, varying in size from a pinhead to a pea, first seen as a rule at the root on the right side, with the mottling more marked on this side until it is generalized on both sides, when this difference becomes less marked. Increased air-intake may account for this right side predominance. The apices and bases are always less involved. The definition of the nodules varies with the quality and quantity of dust and the rate of fibrosis. In the second stage there is definite interference with diaphragmatic excursion. Except possibly in metallic dust fibrosis, the cause of the nodular shadows is the fibrosis rather than the pigment content. A superimposed tuberculosis in the second stage of pneumoconiosis may be quite difficult of differentiation, but the fact that in this stage the apices are relatively clear and only lately involved helps considerably. The third stage the authors describe as one characterized by a diffuse fibrosis which can be divided into three appearances: The first, a coalescence of large nodules into larger masses. Secondly, a more or less diffuse fibrosis with evidence of definite nodules still present, simulating pulmonary tuberculosis very closely. The third is one of massive fibrosis appearing as extensive pulmonary consolidation, usually one area in each lung or more than one, or occasionally unilateral. These masses are usually well within the lung but may extend to the periphery, with thickened overlying pleura. The diffuse fibrosis of the third stage is likely a result of conglomeration of the small nodular fibrosis of the second stage or an advanced interstitial fibrosis or both, with one more marked than the other. A review of literature shows that tuberculosis is an important factor coincident with pneumoconiosis, and although in some instances it may seem less progressive in this condition than in more normal lungs, most series show a definite increase in tuberculosis in silicotic lungs. There does seem to be some protection against tuberculosis in coal miners, at least the incidence is much lower than in other miners, but the cause is yet not satisfactorily explained. In their study of the different dusty industries, the authors found that where the dust contains a large amount of silica the silicosis develops more rapidly, and the incident tuberculosis is more dangerous. In granite cutters the changes appear early and these have been extensively described by Jarvis. In potters the silicosis takes place more slowly than in hard rock miners. In metal grinders pneumoconiosis may develop early, but whether this is due to metallic dust or dust of abrasives is yet open to question. There are definite cases recorded of metallic dust fibrosis. In brick workers the fibrosis varies considerably according to the type of brick made, depending again upon the silica percentage of the

materials. A cement factory is very dusty but relatively harmless because of the low silica percentage. Asbestos workers are subjected to much dust, with rather high per cent of silica, and the fibrosis is more marked and rapid. Carborundum dust consists of very fine particles, so is suitable for cellular disposition, but opinion still varies as to the role it plays in pneumoconiosis. Lime dust is soluble in the body fluids, therefore causes very little fibrosis. Organic dusts may produce some fibrosis, but this possibly is due to their inorganic content and action as irritants to the lung tissue.

Congenital Diaphragmatic Hernia with a Report of Seven Cases with Autopsies.—Congenital hernia of the diaphragm was reported as early as 1698. Prior to 1908 the condition had not been recognized during life in more than ten instances. UNGER and SPEISER (*Am. J. Roent. and Rad. Therap.*, 1926, 15, 135) discuss three varieties: (1) False congenital, by far the most common, where the contents pass directly through a congenital opening as through a dilated normal opening; (2) true congenital, where a definite sac made up of a thin layer of pleura and a layer of peritoneum precede the hernial contents into the thorax; (3) diaphragmatic eventration, a condition of chronic, idiopathic, unilateral elevation of the diaphragm. The false result from an impediment of the normal closure of the diaphragm during intra-uterine life. Certain regions are commonly the site of congenital hernias, due to an arrest or defect in development: (1) A triangular area between the pars sternalis and pars costalis (Larrey's space or foramen Morgagni). (2) A space on either side between the pars vertebralis and pars costalis (foramen Bochdaleki); the most plausible theory is that of Laterjet and Jaricot, that that portion of the diaphragm is the last to close, is the most poorly vascularized and only a slight degree of abnormal pressure here would suffice to cause nutritional disturbances with a resulting arrest of development. (3) The opening through which the sympathetic nerve passes. (4) At the hiatus esophagus. The left half of the diaphragm is most commonly involved. Roentgen ray examination will differentiate between eventration and hernia; in the former the abdominal content will always be below the diaphragm. Nearly half die at birth or shortly afterward, some live for a few months or years but suffer chronic embarrassment of respiration, while others show few definite symptoms during life.

Roentgenologic Exploration of the Bronchial Tubes with Iodized Oil (Lipiodol).—Lipiodol is vegetable iodized oil, containing 40 per cent of iodine; a definite chemical compound in which the halogen cannot be detected by ordinary reactives. FORRESTIER (*Radiology*, 1926, 6, 303) reasons this is the explanation of its being tolerated in the cavities of the body, as it contains no free iodine. With age or exposure to light it becomes brownish, this change denoting decomposition and liberation of free iodine; in such condition it should not be used. In January, 1922, following its use in cavities of the spine, epidural and subarachnoid spaces, it was found to be well tolerated by the respiratory mucous membrane, and, after intratracheal injections films of the bronchial tubes of a living subject were secured. Injected into the bronchial tubes, lipiodol is quickly absorbed; shadows are seen immediately

after injection and gradually disappear during the following days. Part of the oil is expectorated within a few hours; the remaining part is absorbed by the mucous membrane. The daily elimination of iodine during the first fortnight is about 2 cgm.; the last part, about one-tenth, is visible on roentgenograms for several weeks. Following intratracheal anesthesia, 20 to 40 cc. of lipiodol, warmed to body temperature, are injected. The injection is performed by use of a long, curved catheter, the end of which must be pushed down through the glottis into the trachea. For the exploration of the base of the lungs the author puts the patient in the sitting position, for the middle lobe the recumbent position and for the apex the recumbent position, the nearer shoulder being as low as possible. In most cases it is better to explore one lung at a time. Roentgenograms in different positions and stereoscopic views should be taken as soon as possible after the injection of the lipiodol. Coughing commences after twenty minutes and roentgenograms taken after several coughing spells have lost their accuracy. The injection may be repeated as often as necessary. The subglottic, with a curved needle stuck directly into the trachea in the midline of the neck; the laryngoscopic, a gum or metallic catheter introduced into the trachea; the bronchoscopic methods are also used. The method is indicated when: (a) A deviation, stricture or abnormality of the trachea is suspected; (b) the diagnosis between phthisis and bronchiectasis is difficult in patients with a long-standing pulmonary disorder and chronic expectoration; (c) after a vomica, which indicates a cavity in communication with the trachea; (d) to determine the origin of thoracic fistulas; (e) in all cases where other clinical and laboratory methods fail in a clear diagnosis. Deviations of the trachea may be differentiated from open cavities; the presence of a lung tumor does not allow the lipiodol to enter the corresponding bronchi; the absence of penetration of the lipiodol into a lobe is an aid in the diagnosis of marked pathologic change. In cases of lung compression by a thoracic or pleural growth the stoppage of the lipiodol in the lobules and bronchi at the periphery of the growth is characteristic. The cavities of the lung may be localized exactly, their shapes and volumes clearly delineated, provided they are in communication with the bronchial tubes. The method has been most useful in the diagnosis of bronchiectasis, particularly in showing pathologic changes hidden by the heart shadow. After therapeutic pneumothorax exploration with lipiodol may give information, in pleural adhesions showing whether these are plain membrane, or contain fragments of lung; in the latter cauterization is contraindicated because of ensuing fistulas. Accidents are rare; some few patients showed a transitory iodism. This can be avoided by having the patients expectorate and not swallow the oil when coughing. Contraindications include hemoptysis, in which a few days should elapse before injection. The injection is not to be attempted in febrile, tuberculous patients. Only the transglottic method should be used in patients with pulmonary gangrene or any anaërobic infection of the respiratory tract. The administration of lipiodol has benefited patients with much expectoration, decreasing the quantity of sputum for weeks and even months, and it is to be hoped that a certain therapeutic result may be produced by this harmless and powerful local iodine treatment. An experience of four years has proved it to be harmless and in some cases of therapeutic value.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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A Search for an Ideal Antigen for Therapeutic Immunization.—The many disadvantages of the antigens used in therapeutic immunization have stimulated the search for more ideal substances. The work of Besredka with his theory of local immunity is well known. This author used in dressings as well as for injections bacterial vaccines or culture filtrates, and the immunity developed was not accompanied by demonstrable antibodies. More recently HORDER and FERRY (*Brit. Med. J.*, 1926, 2, 177) have reported certain clinical results with "ectoantigens" or "immunogens." This is the centrifugate of a bacterial suspension. The best results were obtained with suspensions of cultures of twenty-four hours or less. The work is largely based upon earlier experimental studies undertaken by FERRY and FISHER (*Brit. J. Exper. Path.*, 1924, 5, 185; *J. Lab. and Clin. Med.*, 1925, 10, 817) following Horder's suggestions and the details of the investigation are to be found in these articles. The nitrogen content of the antigens is very low and high titer antibodies (agglutinin and complement-fixing bodies) are developed in the animal body, thus differing from the findings of Besredka and his school. These antigens are not believed to be exotoxins or endotoxins, but rather some form of solution of the ectoplasm of the bacteria. They are, moreover, practically nontoxic. Promising results have been had with antigens of this type for streptococcus, pneumococcus and gonococcus infections. The authors also review very concisely the various types of antigens which have been used for therapeutic immunization.

Reinfection with Tubercle Bacillus in the Guinea Pig.—The problem of reinfection in tuberculosis has received much attention for many years. PARAF (*Compt. rend. Soc. de biol.*, 1926, 95, 1182), continuing his previous work on the same subject, inoculated one series of guinea pigs with 0.001 mg. of *Bacillus tuberculosis* each day for fifteen days and another series with the same daily dose for eight days, then an interval of eight to sixteen days and a further eight days of inoculation. All the animals received the same total dose (0.015 mg.). A difference in the time of death indicated that the interrupted inoculations were more rapidly fatal than the continuous. The deaths under interrupted treatment were as follows: In the first month, 6; during the second, 32; in the third, 15; in the fourth, 5; as contrasted with those following the continuous treatment, viz: In the first month, 7;

in the second, 12; in the third, 10; in the fourth, 26; in the fifth, 3; in the sixth, 5. The author points out that these results conform with the inhalation experiments of Grysez and Petit-Dutaillis, which demonstrated that repeated but continuous inhalations are less dangerous than a single massive inhalation. They are also parallel with the clinical fact that contacts with tuberculous parents, interrupted and then repeated, are more dangerous for the infants than contacts just as long but continuous.

The Anatomical Structure of Tubercle from Histogenesis to Cavity.—In a review upon the development of tuberculous lesions. KRAUSE (*Am. Rev. Tuber.*, 1927, 15, 137) points out that the tubercle bacillus of various sources is able to live and multiply in the tissues of a variety of animals. This organism is at the same time highly resistant to outside influences because of the protection afforded by the high lipid content. This lipid is in the nature of a wax combined with protein. When they settle in the body for the first time, the tissues react to their presence by forming nodular tubercles. The reaction is one to the lipoids of the bacilli. Nodular tubercle is, therefore, a protective and conservative process, serving to wall off the tubercle bacilli, and set them apart from normal tissue. In fully 90 per cent of tuberculous infections, the nodular tubercle performs its defensive function successfully. Nodular tubercle evolves slowly out of the proliferation of cells *in situ*. With the presence of nodular tubercle in the body, the tissues acquire the capacity of reacting to the protein of the tubercle bacilli. This changed condition of the tissues is called tissue allergy or hypersensitiveness. The allergic reaction brings about nonnodular diffuse tissue changes. It is characterized by a rapid exudation of cellular elements from the blood to form acute inflammations and effusions. Tissue allergy too is a defensive and conservative process. Through prompt inflammatory responses, it serves to stay the more facile progression of tubercle bacilli that takes place in the body of the nonallergic animal. It fixes bacilli where they lodge. After infection has been accomplished, it serves as the body's chief instrument against the unrestrained dissemination of infection. The inflammatory allergic reaction tends to stimulate greatly the powers of nodular tubercle to form fibrous tissue. The tissues will also react to form tubercle around inert nonbacterial foreign bodies. They treat the extracted lipoids and dead tubercle bacilli in a similar manner. Structurally and anatomically such a result constitutes tuberculosis. But living tubercle bacilli lead to the development of a parasitic invasive reaction with potentially unlimited powers of extension and progression. When animals become tuberculous, their allergic tissues respond to the dissociated proteins of tubercle bacilli (tuberculins) with acute inflammation and its sequelæ (necrosis and fibrous tissue). Anatomically, both tuberculins and dead tubercle bacilli evoke the diffuse formations of tuberculosis. Tubercle formation may be looked upon as a composite effect of lipoids and proteins of the microorganism concerned. The disease tuberculosis is based upon the extension and progression and repetition of tubercle formation. The ultimate issue of every tuberculous focus turns upon the balance struck between central necrosis and fibrosis. Necrosis of tubercle is a result of allergy—a sequel of the inflammatory reaction. It begins centrally

and extends outward. Fibrosis is brought about through the conversion of epithelioid cells of nodular tubercle into cells of fibroblastic type. It is greatly enhanced by the allergic inflammatory reaction as the latter subsides. It begins at the periphery and extends inward. From the point of view of bodily economy the most important element of tuberculous processes is the integrity and competence of their fibrous investments. They stand between interned bacilli and the body. They also stand between poisonous focal products and the body.

Rupture of the Aorta and Dissecting Aneurysm. — SCHNURBEIN (*Frank. Ztschr. f. Path.*, 1926, 34, 532) reports 3 cases of rupture of the aorta which were associated with dissecting aneurysm. In all there are about 300 cases in the literature. In all cases there are two features to be considered in regard to dissecting aneurysm, first the development of a passage through the intima into the middle coat of the arterial wall, and second the separation of the layers of the artery permitting of the development of a sac within its own tissues. In a certain proportion of cases the lesion in the intima admitting the passage of blood consists of an atheromatous erosion. This condition commonly presents itself in advanced years. However, a certain proportion do not present a primary defect of the intima and this inner coat is torn through owing to an unusual weakness of the media. At times this rupture is associated with undue strain thrust upon the artery, but again it may appear in the absence of undue intraarterial pressure. Two of the cases reported by the author belong to the usual type of dissecting aneurysm occurring in elderly individuals. The third case was that of a man aged thirty-eight years who showed the presence of a healed dissecting aneurysm, death having occurred from cardiac weakness. The entrance to the dissecting aneurysm was through a tear immediately above the aortic valves. The author notes that a hyaline degeneration occupies some of the tissues of the media and may account for the weakness admitting of the production of the dissecting aneurysm. It is interesting that in this case a second and more recent dissecting aneurysm was also found. The author is unable to indicate the exact manner in which these dissecting aneurysms make their appearance, although in all cases of this condition the lesion is dependent upon an injury of the media. He was unable to demonstrate the nature of these changes, and the conditions which brought them about.

Concerning Experimental Fowl Sarcoma. — During recent years, numerous investigators have been studying the principles involved in the transplantation of the Rous chicken sarcoma. This tumor can be very easily transplanted from one animal to another. It has also been found that the tumor may be dried and reduced to a powder while still maintaining its capacity for producing new tumors in fowl. Furthermore an emulsion of this dry powder can be filtered giving rise to a clear filtrate which likewise will give positive results. NAKHARA (*Cent. f. Allge. Path.*, 1927, 39, 103) investigated this tumor powder and found that upon making emulsions of it he was able to demonstrate cells having all the characteristics of living structures. He believed that they represented some of the original sarcoma cells. However, when such an emulsion was treated with 50 per cent alcohol, or was heated

to 60° C., he no longer could demonstrate these cells in his preparations. Upon making cultures *in vitro* of this powder he observed the presence of living cells extending in a radial fashion through the medium. He likewise observed that in 50 per cent glycerin emulsion intact living cells were still present. It is interesting that the tumor cells suspended in an emulsion will pass through a Berkefeld filter and can be demonstrated in the filtrate. The author further believes that the evidence, as has been brought forward by some authors, of the presence of specific agents inducing sarcoma, is fallacious in the presence of living tumor cells in the material which was used.

HYGIENE AND PUBLIC HEALTH

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Six Additional Cases of Laboratory Infection of Tularemia in Man.—SPENCER and PARKER (*Public Health Reports*, 1926, 41, 1341) report 6 new cases of laboratory infections of tularemia occurring at Hamilton, Montana. Only two of the 8 persons who became ill were engaged in handling infected laboratory animals or infected ticks escaped. In none of these cases was there any evidence of local lesion to suggest a site of entrance of the infection. The cases resembled typhoid fever more than anything else. The diagnosis was established by serological means—agglutination of culture of *Bacterium tularensis*. Eruptions occurred in 2 cases. Two cases had sore throat, 2 cases showed relapse after ten months and eight months, respectively.

A Review of the Work of the United States Public Health Service in Investigations of Stream Pollution.—FROST (*U. S. Pub. Health Repts.*, 1926, 41, 75) reviews the work on the sanitary aspects of streams over a period of about twenty-five years, since the beginning of systematic studies. The fields of research and application falling to Federal authorities on one hand and to state and local authorities on the other are defined. It is pointed out that sewage from cities is usually discharged, without treatment, into streams. Generally, cities lower down drawing their supplies from these streams are able to effect satisfactory treatment by the application of recognized means of purification. It is predicted that in the future other measures will need to be taken as city populations continue to grow and the degree of pollution of streams becomes higher. The subject is complex from both scientific and administrative points of view. A comprehensive plan to meet the situation must be based on suitable data on: (1) The

quality of water delivered to consumers—certainly safe but not unnecessarily rigid; (2) knowledge of reliability and efficiency of purification process; (3) knowledge as to degree of pollution furnished by various communities and the effectiveness of the operation of natural purifying processes. It is to furnish data on such questions that present studies are being directed.

A Case of Tularemia in a Laboratory Worker. — DIETER (*Public Health Reports*, 1926, 41, 1355-1356) reports an additional case, making a total of 18 now on record of laboratory of infection of tularemia. In the present case, the strain came originally from wild rats which were being examined for plague. In this case there was a local lesion on the finger which may have been the site of infection, though this was not proven.

Degree of Mental Deficiency Resulting from Congenital Syphilis. — DAYTON (*J. Am. Med. Assn.*, 1926, 87, 907) finds the intelligence of 61 patients with mental deficiency with congenital syphilis definitely above that in 1956 cases due to other causes. He states that when congenital syphilis initiates the pathologic process resulting in mental deficiency, the process is less severe, and a higher average of intelligence is attained than in cases with other causation. From the statistical point of view, congenital syphilis does not produce large numbers of cases of mental deficiency. When we consider the intelligence, congenital syphilis does not produce a low grade of defect. Therefore, from both the quantitative and the qualitative points of view, congenital syphilis is not a serious factor in the production of mental deficiency.

A State-wide Smallpox Survey in Tennessee. — BREEDING and LANE (*U. S. Pub. Health Rep.*, 1926, 41, 1511) report that in Tennessee smallpox has varied in the past ten years from 7.8 per 100,000 in 1916 to 139 in 1918, and 130 in 1924. In spite of laxity in enforcement of vaccination the incidence has not been so high as might have been expected. First-hand information was secured regarding the smallpox situation throughout Tennessee, the approximate number of immune persons, the cost of control measures, the sentiment of the county officials and the general population with regard to vaccination, and the difficulties most frequently encountered by health officers in the enforcement of vaccination regulations. From an educational standpoint, the survey served to impress the gravity of the situation upon the local authorities and stimulated their interest. Although the expected increase in the incidence of smallpox over the previous year did not occur, had it occurred and had intensive control measures been necessary the educational work accomplished and the closer contact made between the State department and local health authorities would have greatly facilitated the enforcement of such measures. Although the percentage of persons vaccinated in Tennessee is extremely low, it is believed that the State law empowering local boards to enact such vaccination measures as may be deemed necessary for the protection of the public is adequate for the time being. A State compulsory vaccination law, unenforceable in rural sections, might stir up such opposition as to hinder other health programs. By virtue of the present law, local officials have, in times of epidemics, enforced vaccination of con-

tacts, of the inhabitants of a zone around the foci of infection, and of the school population with little or no opposition. Greater reliance should, for the present, be placed on educational measures to secure more widespread vaccination. While the State health department should keep the local authorities informed and make suitable recommendations from time to time, with a State the size of Tennessee the ultimate solution of this problem, as well as of many rural health problems, would seem to lie in the extension of wholetime county health departments. Smallpox offers no serious problem to counties with such departments. There seems to be a growing sentiment in the medical profession of the State, and especially among health officers, that quarantine measures are often ineffectual and that persons refusing vaccination on the grounds of restriction of personal liberty or otherwise should not be compelled to subject themselves to quarantine restriction. It is argued that such a course would emphasize the importance of vaccination and encourage its practice. Until, however, we can secure vaccination of all minors and irresponsible persons, until vaccination is an equal protection against the most severe as well as the milder forms of the disease, and until vaccination becomes an absolutely reliable procedure, with the use in every case of a vaccine of unquestionable potency and the most approved technique followed by a careful reading and an accurate interpretation of the result, the elimination of the strictest possible quarantine is inadvisable.

A National Program for the Unification of Milk Control.—FRANK (*Pub. Health Rep.*, 1926, 41, 1583) reports on the progress in milk sanitation during several years. His own survey of milk-borne outbreaks for five years shows about 19 per cent in the United States. Enteric fevers stand first in number, followed by scarlet fever, diphtheria, septic sore throat, and dysentery. The advantages of uniform methods of control and uniform ordinances is pointed out, and the point stressed that in the variety now in vogue some might be wrong. It is held that conflicting methods of control have kept milk consumption below a desirable point. The relation of uniformity in requirements to interstate shipment is pointed out. Safe milk is defined as "both properly produced and perfectly Pasteurized" which places two safeguards between consumer and producer, as respects infectious diseases. It is recognized that practically ideal supplies are not to be had and provision is made for safeguarding three grades of Pasteurized milk and one of raw.

The Radioactivity of Natural Waters.—COLLINS (*U. S. Pub. Health Rep.*, 1926, 41, 1937) a chemist of the Water Supply Division of the U. S. Geological Survey, states that all natural water is more or less radioactive and that this property is being exploited in some instances when in reality it is no more unique than the wetness of the same water. Results of laboratory tests on water are given. The following is the final paragraph: "The best available evidence based on scientific studies of the treatment of disease with radium emanation, on measurements of radioactivity of natural spring waters, and on the reported uses of the spring waters, leads to the conclusion that, up to this time, it has not been shown that the small amounts of radioactivity found in natural waters have any effect on the medicinal value of the waters."

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 25, 1927

On the Postnatal Growth in the Area of the Optic Nerve in Albino and in Gray Norway Rats.—H. H. DONALDSON and C. C. WANG (from the Wistar Institute of the University of Pennsylvania). It is generally recognized that the visual apparatus in the albino rat is somewhat defective as compared with that in the gray Norway. To obtain more precise information along this line, the area of the cross-section of the optic nerve was determined from birth to maturity in both sexes of these two races. When the brain weight of the albinos is raised to that of the Norways it is found that the areas in the two races are alike. The most marked distinction in area is between the sexes, the female optic nerve having a greater area in both races. The female eyeball is larger than that of the male, but the difference is not quantitatively sufficient to account for the difference in area. On the other hand, the gray Norway, with larger optic areas, has smaller eyeballs than the albino, with smaller areas. An explanation of this relation is lacking. These observations show that albinism has not modified the area of the optic nerve in relation to the weight of the brain, but that in both races the area of the optic nerve is greater in the female.

A Chemical Study of Thymus Involution.—FREDERICK S. HAMMETT (from the Wistar Institute of Anatomy and Biology, Philadelphia). The thymus of female albino rats 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 115, 130, 150, 175 and 200 days of age was allowed to autolyse in normal saline buffered to pH 7.4 at 37.5° C. for six hours. The initial and terminal amino acid-content was determined according to the gasometric method of van Slyke. It was found that the rate of autolysis, as determined by the percentage increment in amino acids per unit weight of thymus tissue, was increased during the period when the thymus was undergoing involution in the body. This suggests that thymus involution is an endogenously conditioned acceleration of proteolysis. The basis of the change in enzymatic activity has yet to be determined.

The Relation of the Inorganic Constituents of a Ration to the Production of Ophthalmia in Rats.—J. H. JONES (from the Department of Physiological Chemistry, University of Pennsylvania School of Medicine). In a series of papers appearing since 1922, McCollum, Simmonds and Becker have described the production of an ophthalmia in rats on diets containing what they thought to be sufficient amounts of vitamin A. They have advanced various theories as to its cause. In the first paper¹ they thought it was due to an improper balance of the inorganic constituents of the ration. They attempted to show in the second publication² that the eye trouble was in some way associated with a deficiency of vitamin B in addition to the improper salt balance. In

a third paper³ these investigators believe that they have shown a connection between the assimilation of iron and the reproductive factor of vitamin E, both of which are associated with the eye trouble. They claim that if ferric citrate is used as the iron salt the ophthalmia does not develop, but if instead ferrous sulphate is used the animals fail and almost invariably develop sore eyes. However, if materials containing rather liberal amounts of vitamin E are added to the diet containing the ferrous sulphate the eye condition is cured. It has been repeatedly demonstrated that vitamin A is destroyed by oxidation. Since ferrous sulphate is a good catalyst for oxidation reactions at room temperature, it is possible that McCollum and associates were dealing with an actual vitamin A deficiency due to its disappearance from the ration by oxidation; the rate of oxidation being accelerated by the presence of ferrous sulphate. With this in mind experiments were begun in the fall of 1925 to test this hypothesis. The vitamin A in butter fat will remain potent almost indefinitely if the butter is kept in a solid mass and in a cool place. If, however, a small quantity of the butter fat is mixed with a dry ration, air can mingle with it intimately. Under these conditions it is possible that vitamin A could be destroyed by atmospheric oxidation. Destruction of the vitamin in this manner could be prevented in part by preparing the rations at frequent intervals. We have, therefore, compared rations made up in quantities sufficient to last several weeks with those lasting only a few days. The feeding in each case was begun immediately after the ration was prepared. Rats which were fed the McCollum ration that was prepared in quantities sufficient to last about five days grew almost normally, and during a period of six months showed no signs of ophthalmia. Several of the females reproduced but none of the young lived more than one or two days. When, however, the same ration was prepared in quantities sufficient to last from four to six weeks, the animals grew for a while, then developed sore eyes, lost in weight, and died about the tenth week. Ophthalmia developed about two weeks sooner if the amount of ferrous sulphate in the ration was doubled. When the salt mixture containing ferrous sulphate was reduced from the original level of 4.1 per cent to 2 per cent of the ration the animals grew for a longer time and ophthalmia made its first appearance in about eighteen weeks instead of eight. When, however, the ferrous sulphate of the ration was increased so that the animals which were fed the salt mixture at the 2 per cent level received the same amount of ferrous sulphate as those fed the salt mixture at the 4.1 per cent level, they developed ophthalmia in about eight weeks with subsequent loss of weight and death. These experiments indicate that this condition is not a hitherto unknown type of nutritive disturbance. Likewise there has not been demonstrated a relation of iron assimilation to any of the vitamins. Instead the condition is one of simple vitamin A deficiency caused by the oxidative destruction of the vitamin in the ration. The rate of oxidation is increased by the catalytic action of ferrous sulphate.

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The Extension of the Debye-Hückel Theory to Hemoglobin Solutions.—W. C. STADIE and E. R. HAWES (from the John Herr Müsser Department of Research Medicine of the University of Pennsylvania). In a very dilute solution of a salt the laws for ideal gases hold: *e. g.* the osmotic pressure is $P = R T C$ ($C = \text{conc.}$). In more concentrated solutions, *i. e.*, 0.005 moles per liter, the simple laws do not hold. If, however, the concentration is multiplied by an activity coefficient f giving the *activity*, *i. e.*, $a = fC$, then $P = R T fC$ holds at all concentrations.

This paper reports a study of the activity coefficient of the bicarbonate ion in the presence of NaCl and hemoglobin. It was found that NaCl had an effect on the behavior of HCO_3 and hemoglobin had a similar effect and further that the various analogs of hemoglobin, *e. g.*, reduced hemoglobin, carbon monoxid hemoglobin, cyanhemoglobin, etc., influenced the HCO_3 differently, *i. e.*, they had specific effects. The effect noted was a diminution in the activity coefficient $f\text{HCO}_3$. To explain this effect of NaCl and the various hemoglobin pigments, the Debye-Hückel theory of solutions was extended to protein solutions. Debye and Hückel, two mathematical physicists at Zurich published in a series of papers (1923-1926) a theory which explains in a highly satisfactory manner the behavior of concentrated salt solutions. For example, it enables one to calculate (within limits) such properties as osmotic pressure, membrane equilibria, solubilities, etc., provided one knows (1) the diameter of the ions of the salt and (2) the dielectric constant (capacity to absorb electricity) of the solvent. The behavior of the bicarbonate ion as expressed by the activity coefficient was found to be in accord with the theory and the data allowed of the calculation of the (1) size of the bicarbonate ion and (2) the dielectric constant of the hemoglobin solution. In general the calculated ion size agreed with independent measurements but there is insufficient data at hand to check the dielectric constants obtained.

The Rate of Penetration of the Erythrocyte by Certain Substances.—M. H. JACOBS (from the Department of Physiology, University of Pennsylvania, Philadelphia, Pa.).

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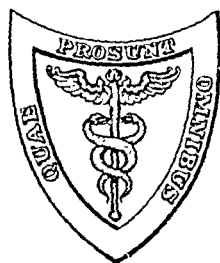
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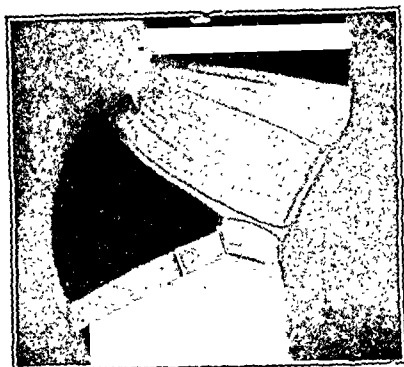
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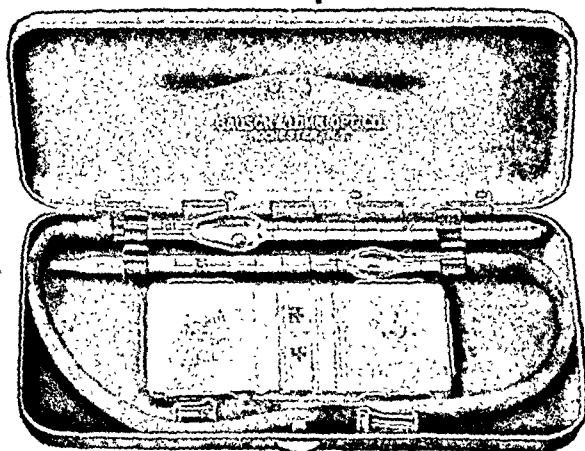
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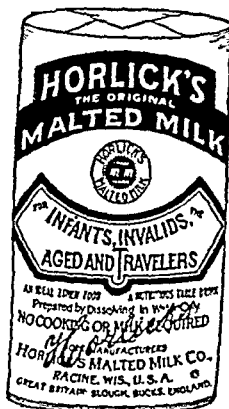
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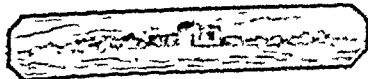
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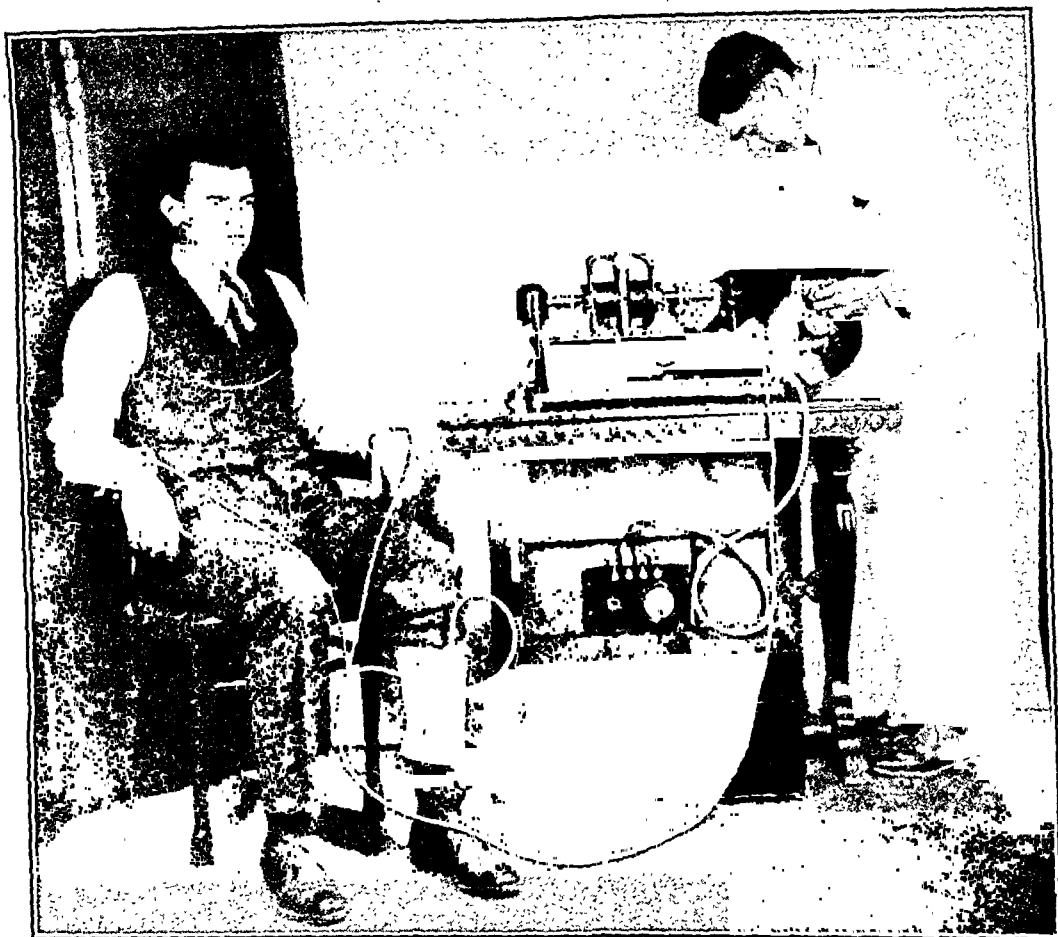
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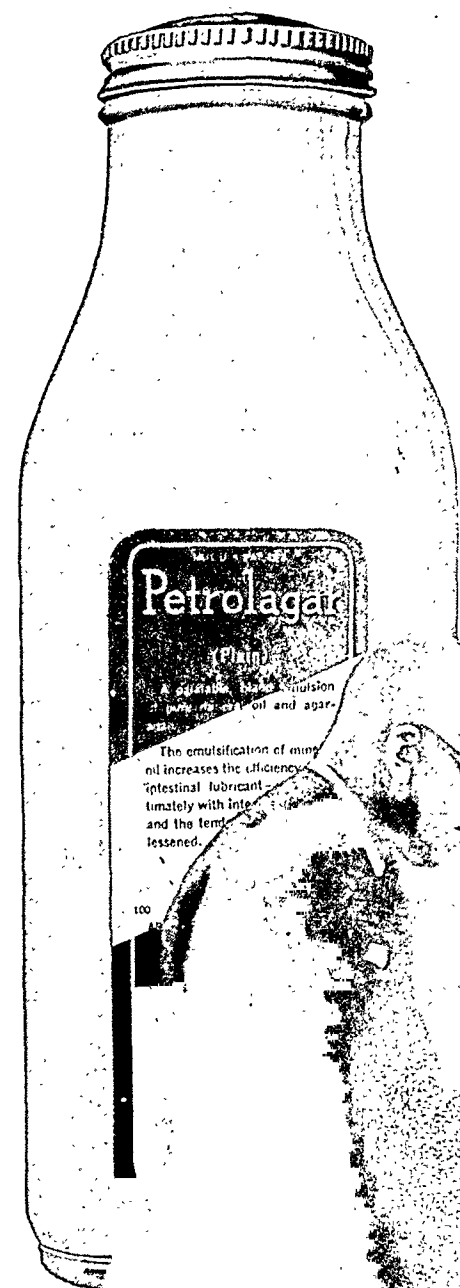
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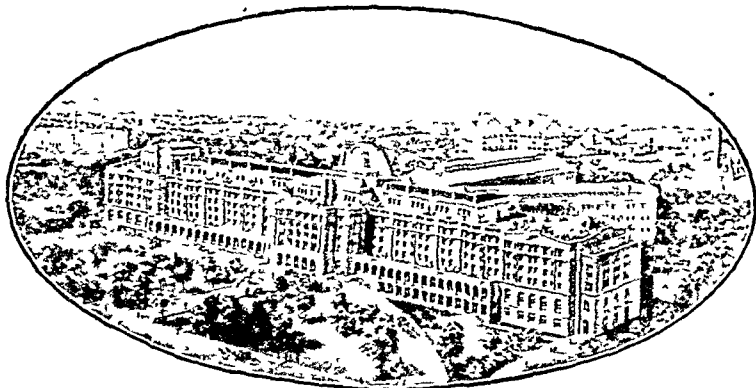
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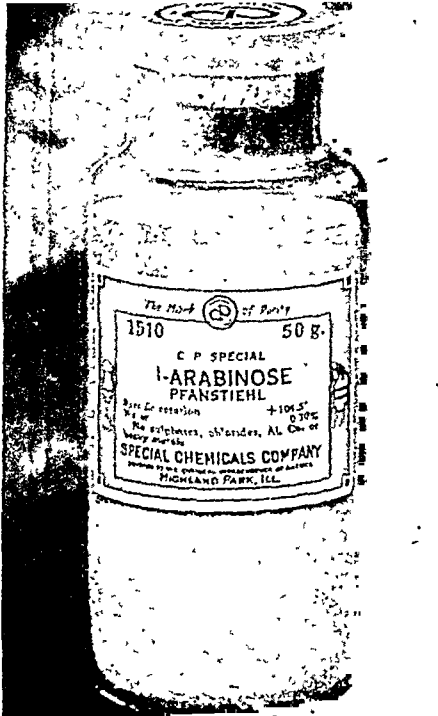


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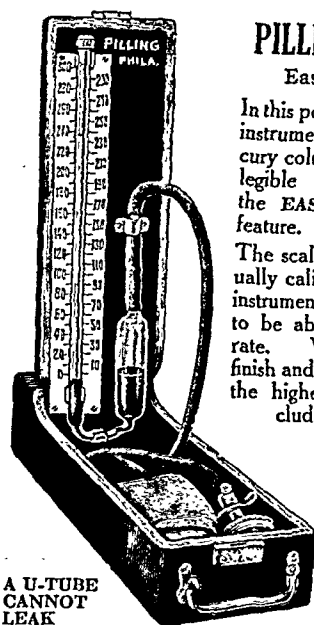
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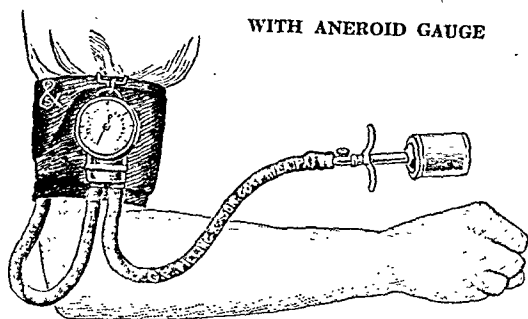
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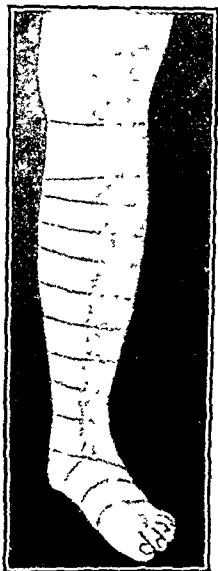
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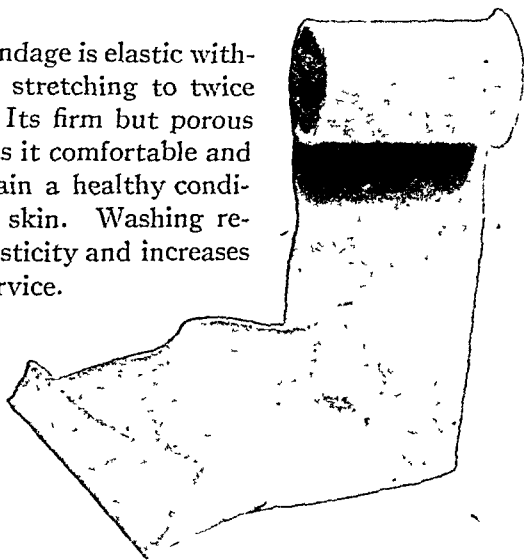
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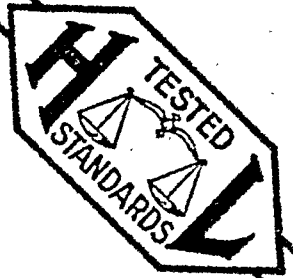
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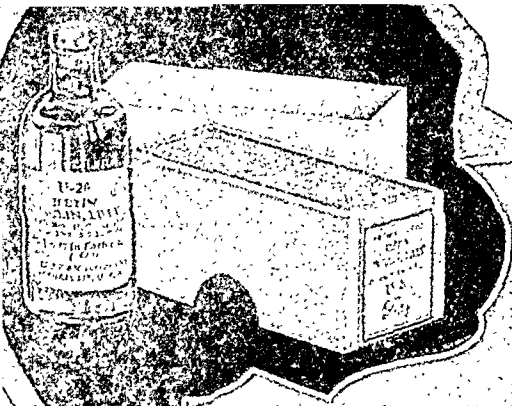
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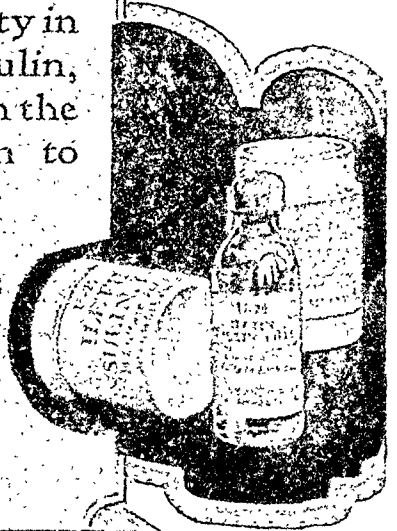
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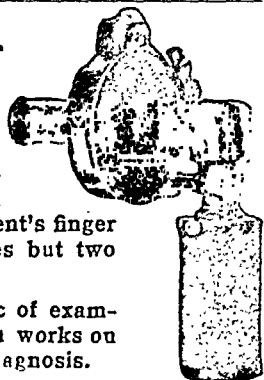
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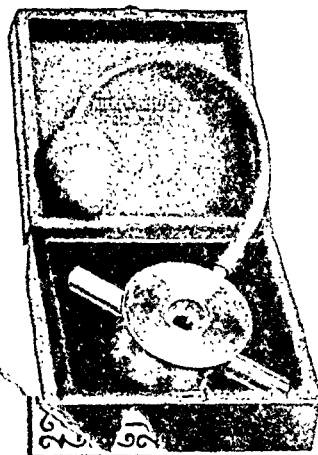
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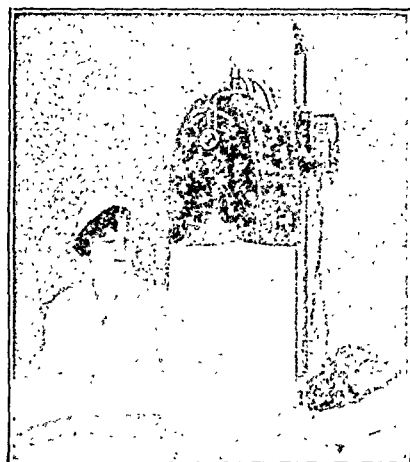
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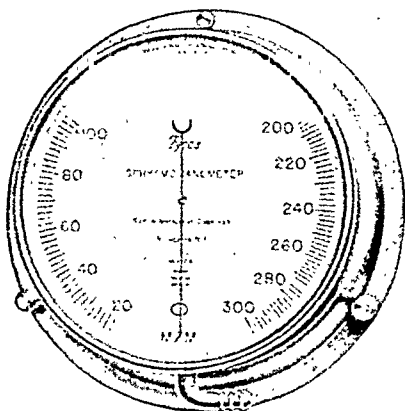
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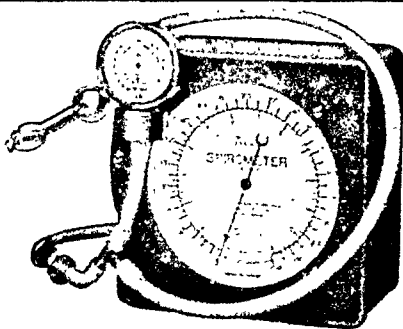
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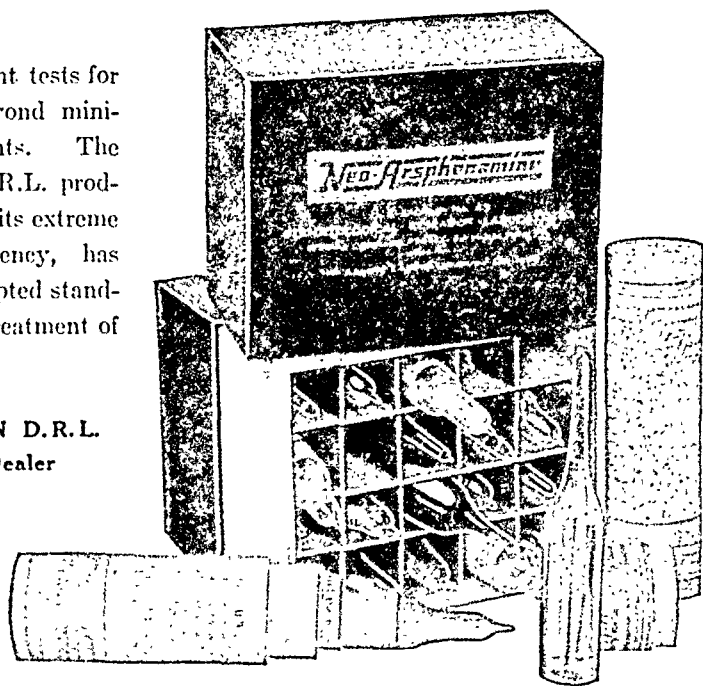
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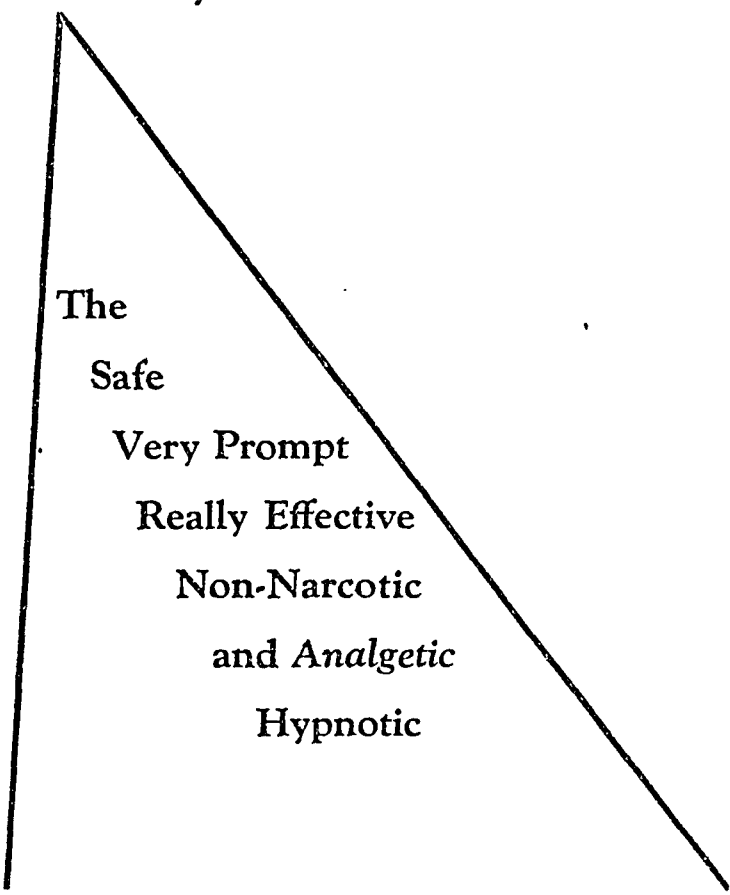
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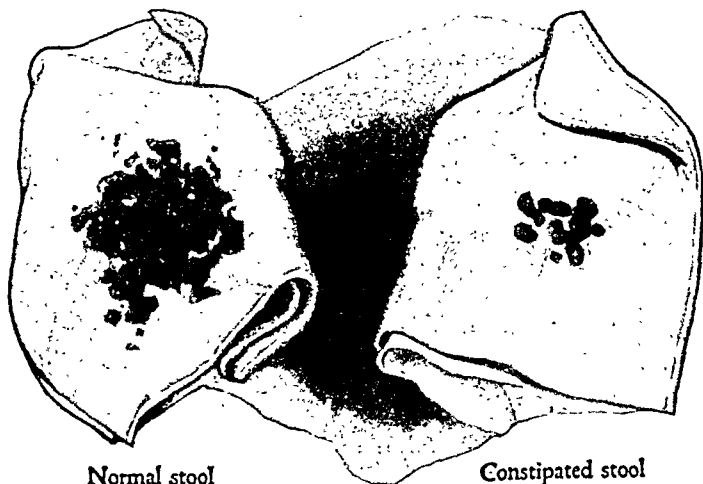
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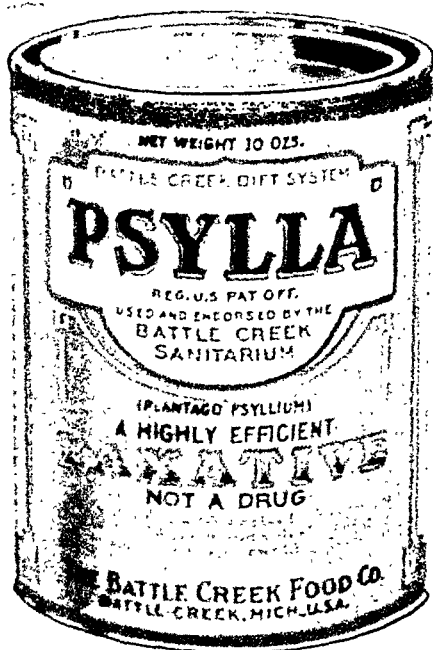
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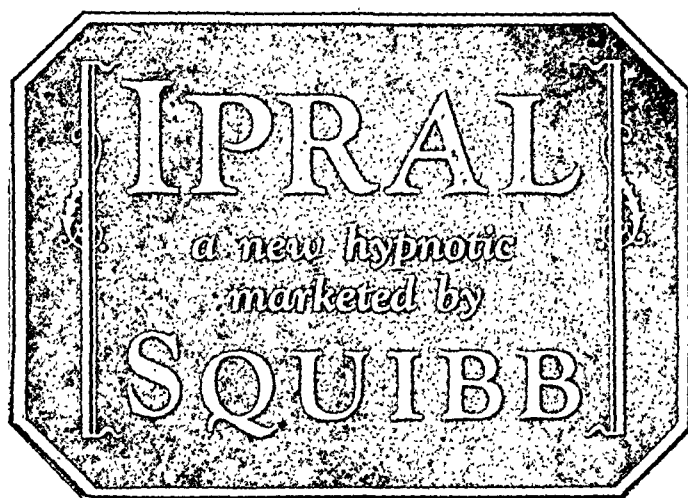
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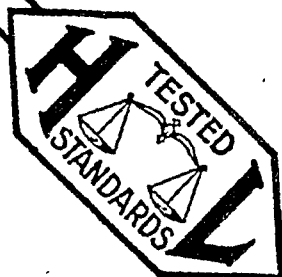
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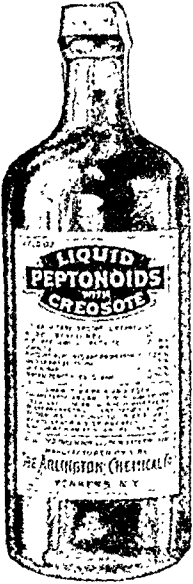
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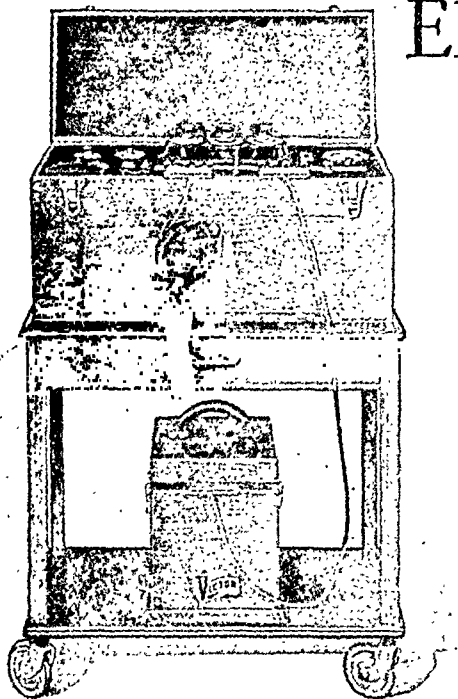
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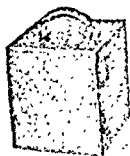
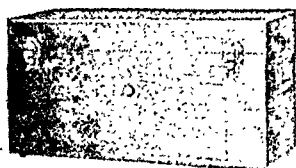
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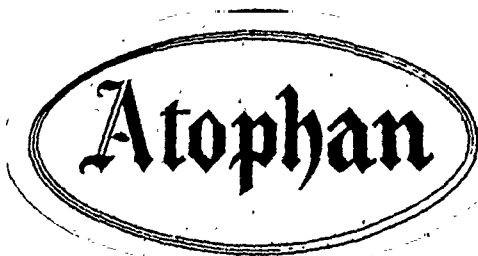
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FEBRUARY, 1927

ORIGINAL ARTICLES.

URETERAL STRICTURE: THE ETIOLOGY, DIAGNOSIS,
PATHOLOGY AND TREATMENT OF A NEW
ABDOMINAL SYNDROME.*

BY GUY L. HUNNER, M.D.,

ASSOCIATE PROFESSOR IN CLINICAL GYNECOLOGY, JOHNS HOPKINS UNIVERSITY MEDICAL
SCHOOL.

SKEPTICISM and the adoption of a new idea only after a reasonable demonstration of its practical value are signs of a healthy attitude in medical practice. Rejection of a theory because of its novelty or because its acceptance leads to the overthrow of traditional views and practice may indicate a state of smugness or self-complacency which in some fields may be condoned without argument, but which in medicine may cause serious injury to the patient, who has entrusted the physician with the care of his health.

Although Fitz of Boston published his epoch-making paper on appendicitis in 1886, some of us are old enough to remember many shocking disasters occurring in the early years of this century because in the minds of some medical men acute appendicitis was still a novel idea and looked upon almost as an obsession of the surgeons. Indeed, it was only when the layman had experienced some of these disasters in his own, or in his neighbor's family, and had thus learned to suspect acute appendicitis and to carry his case direct to the surgeon, that some of the more conservative members of our profession awakened and added this disease to their daily reckoning with acute abdominal disorders. But, although,

* Read at the Philadelphia Academy of Surgery, February 3, 1926.
VOL. 173, NO. 2.—FEBRUARY, 1927

fortunately the disease whose syndrome we are discussing rarely leads to such immediate disasters as so often occur in cases of acute appendicitis, it is certain that ureteral stricture is an abdominal disease of sufficient importance to warrant our making some comparisons between the two conditions.

As a gynecologist, I naturally have far fewer appendicitis patients referred for diagnosis and treatment than the general surgeon, and I am not in a position to judge from personal experience regarding the relative incidence of this disease. As yet our hospital records are not helpful in comparing the incidence of ureteral stricture with that of appendicitis, because in most hospitals ureteral stricture is not being systematically diagnosed.

Because of the early diagnosis and surgical treatment of most cases of appendicitis, and because of the neglect of proper diagnosis in most patients suffering with ureteral stricture, one is justified in stating that today ureteral stricture as a source of incapacity and morbidity ranks equally with or perhaps above appendicitis. Ureteral stricture as treated, or rather, as neglected today, is not only responsible for the physical discomfort and incapacity which it directly causes, but must also be charged with the results of mistaken diagnoses. To make this plain, I need present only a partial list of the evil consequences following our neglect of this disease. On the economic side, there is tremendous loss in disability, time, and hospital expense incurred in following various lines of treatment founded on erroneous diagnosis. When such errors lead to multiple abdominal operations, the patient not only suffers the undermining of the nervous system consequent on the operations and repeated disappointments in obtaining results, but she is likely to acquire permanent morbid processes as a result of the operations. And, finally, if we need further presentments to make the indictment impressive, let us add the last and most important count, namely, the resultant damage to the kidney when we fail to make an early diagnosis of ureteral stricture. In the face of these indisputable facts, can, then, the members of our profession in these days of preventive medicine still continue to contemplate these mistakes with equanimity?

At the risk of making my paper seem elementary after all that has been written on the subject, I shall try to help the busy general practitioner to bear in mind the possibility of the existence of this disease in doubtful cases by presenting a brief summary of its etiology and symptomatology in women, founded on an experience with more than 2500 cases studied in the past fifteen years.

Definition. Ureteral stricture is an intrinsic disease of the ureteral wall resulting in narrowing of the lumen, which leads to varying degrees of stasis in the urinary stream.

Etiology. This narrowing may be congenital or acquired. The congenital types probably most often represent anomalies of devel-

opment, but I believe that time and more careful study will eventually prove that some of the congenital cases are caused by inflammatory processes derived through the placental circulation. By far the greater number of ureteral strictures, however, are acquired. We see an occasional stricture of traumatic origin either from a severe accident, a gunshot or stab wound, or from injury at operation or childbirth. Syphilis may be responsible for an occasional case. I have seen one stricture located at the pelvic brim which was apparently secondary to the pressure and inflammatory action of an adherent ovarian cyst. I have seen pressure by uterine fibroids cause hydronephrosis and hydroureter above, but apparently without causing intrinsic disease of the ureteral wall. Adenomyoma as it spreads across the pelvis sometimes involves the ureter causing stasis from encircling pressure. I have never seen a stricture which could be ascribed to the juxtaposition of a pus tube. A fairly large group of ureteral strictures are associated with cancer of the cervix. The inflammatory process in these cases may involve the periureteral tissues more than the ureteral wall itself and may be present at the time of operation, or it may follow the inevitable trauma and infection due to operation. In a new group, of which I have seen several examples, the periureteral and ureteral infiltration in the broad ligament region has apparently followed the use of the cautery or radium, before, during or after the operation. In renal tuberculosis, disease of the ureter is often a secondary manifestation.

As a gynecologist, I have been constantly expecting to see stricture in the broad ligament region which could be ascribed to inflammatory disease of the cervix, but thus far I have not been able to trace this connection.

Simple inflammatory stricture due to a focal infection in some other part of the body is so overwhelmingly frequent, when compared to stricture from all other causes, that we are justified in saying that the disease usually originates from some such focus. The acute infectious diseases of childhood probably leave inflammatory areas in the ureter, the results of which may not be apparent until later in life. Any localized acute or chronic inflammatory process may finally lead to ureteral stricture. Carbuncle, onychia, intestinal, gall bladder, appendix, and bone inflammations probably each account for a certain percentage of stricture cases; but my experience seems to point to the infections about the head as causing by far the largest number of inflammatory conditions in the ureteral wall. My reasons for this view are briefly as follows: (1) A careful history often reveals that the symptoms due to stricture began soon after an attack of tonsillitis, sinusitis, or a dental abscess. (2) Experience has taught me that the treatment of the stricture area is often futile until one has located and eradicated infection in one of these areas. (3) Dilatation of the stricture area may result in cessation of all symptoms, and in the clearing up of a pyelitis, if

present, only to have the patient come back weeks, months, or years later because of the return of all the symptoms following a fresh attack of sinusitis, tonsillitis, or dental inflammation, or after a visit to the dentist. (4) After a tonsillectomy on a patient who has had treatment for stricture we occasionally have the patient complain far more of pain in the ureteral and renal regions than of the local discomforts from the operation. A cystoscopy a few days after the tonsillectomy shows, in some cases with such ureteral reaction, a wide area of edema and redness surrounding the ureteral orifice, in contrast to the normal or approximately normal appearance of the mucosa in all previous examinations. (5) During and after the grippe epidemic of 1918, many of my "cured" stricture patients returned for further treatment after a severe attack of grippe. (6) Another reason for considering ureteral stricture as originating from a focal infection is the fact that it practically always occurs bilaterally. From the fact that most strictures occur in the broad ligament region from 2 to 5 cm. above the bladder, or in the iliac-gland region from 3 to 5 cm. below the pelvic brim, I have advanced the theory that the systemic infection or toxin probably first attacks the lymphatic glands in these regions and later invades the neighboring ureteral wall.

Symptomatology and Diagnosis.—Because our attention has but recently been called to this disease, the general practitioner is likely to consider that it is of rare occurrence and that its symptoms are so vague as to make a diagnosis difficult and available only to the specialist. As a matter of experience, the physician who keeps this disease in mind, when considering any vague abdominal disorder, is surprised at the frequency of its occurrence, and at the ease with which a fairly certain diagnosis is made without the aid of the urologist.

The urologist who is treating ureteral stricture constantly marvels at the number of patients who come to him on the recommendation of other patients, whom he has relieved, and who recognize the symptoms in their friends and send them for treatment over the head of the family physician, who has failed to make a diagnosis; thus repeating the history of what happened in the early days of appendicitis work.

It would be offensive even to hint that the general practitioner is incapable of making a reasonably certain diagnosis in most cases of chronic gall-bladder disease or appendicitis without calling a specialist to help; but careful anamnesis and physical examination in a case of ureteral stricture usually furnish far more clues for an accurate diagnosis than are obtainable in the above two diseases. Probably every man with a reasonably large practice has one or more of these patients on his visiting list, patients who for the most part have been consigned to the group of neurasthenics supposedly in the enjoyment of miserable health. Some of these patients

are decorated with a half dozen abdominal scars, mute or painful testimony to the zeal of surgical and gynecological brethren, who have been trying to aid in making a diagnosis. Others have tried the patience and skill of gastrolgical confrères and are still complaining of the vague abdominal pains, the accumulations of gas, or perchance a continued mucous colitis. Others are wearing the harness of orthopedic colleagues in a fruitless effort to relieve the back, hip and thigh pains. Here and there a rare individual has been sentenced to one or more terms at Saranac, Asheville, or Colorado, in spite of the fact that the most exhaustive clinical methods have failed to reveal signs of tuberculosis, and the patient still complains of a vague indefinite backache located higher than the usual kidney ache, a slight daily rise of temperature, and general malaise and asthenia.

And yet the general practitioner, if he so wills, can learn tomorrow, almost to a certainty, and without the help of a urologist, whether or not one of these trying patients has ureteral stricture as the physical foundation for the so-called neurasthenic condition.

Careful anamnesis elicits in about 75 per cent of these cases a history of bladder trouble. This may be so slight that the patient has not mentioned it, and on the direct question may answer that she has no bladder symptoms, only a slight frequency when she gets nervous or excited, or a frequency at the time of the menstrual period, or in association with a "cold" or sore throat, or with an arthritic attack. From this almost negligible symptom of intermittent frequency, we see all grades of bladder distress up to the condition of complete incontinence of urine in patients in whom we find no other lesion of the urinary tract than a ureteritis, and for whom we obtain perfect relief by dilatation of the ureteral stricture alone, or combined with attention to some area of focal infection if this has not already been treated.

Urinalysis may be most helpful in the diagnosis; sometimes, however, it may be only slightly suggestive, or at times most misleading. In 20 per cent of stricture patients, there is a chronic pyelitis on one or both sides, and the urine will give characteristic findings. In 50 per cent only a few erythrocytes, a few leukocytes, albumin from a slight trace to a large quantity, or casts, or a combination of these elements will be found. Too often in the past such evidences of disease, when found in meager quantity and only on the most painstaking urinalysis, have been considered as of no significance. In the remaining 30 per cent of stricture cases, the urinalysis is completely negative and patients in this group may present symptoms strongly pointing to the urinary tract and yet be sent to the gastroenterologist, the orthopedist, or the exploratory laparotomist for a diagnosis simply because of the negative urinalysis.

Finally, the general practitioner does not need the urologist to aid in making a careful physical examination. In the stricture

patient, as in any other, one may or may not be able to palpate the kidney. In women the right kidney can usually be palpated. The kidney above a stricture is usually, but not always, tender. Even when the kidney cannot be felt, tenderness in the upper flank will usually be elicited.

Palpation of the ureter where it crosses the pelvic brim practically always elicits tenderness in stricture patients. Frequently the patient will refer discomfort so caused to the epigastrium and complain of nausea, or "that old gas pain;" or the discomfort is referred down the ureter to the "ovaries" or to the bladder with a desire to void.

Palpation of the ureter in the broad ligament region usually distinguishes the area of greatest tenderness. The pain may be referred to any portion of the upper ureter, and even to the kidney. The patient often volunteers: "That is the old bladder pressure" or "That is the pressure on the bowel," or "That is my menstrual pain," or "That is the pain I have when using the douche nozzle," or "That is the pain I have with the sexual act." Dyspareunia in the majority of cases is due to the presence of ureteral stricture, and "ovarian neuralgia" is probably more often a ureteral than an ovarian pain. When a patient complains of "falling of the womb" and you find on taking her history and examining her that she is a nullipara, or that she has an outlet in an excellent state of preservation, and apparently normal internal genitalia in normally high position, do not fail to palpate the ureters for the source of her symptoms, for this maneuver often elicits the "falling of the womb" sensation.

Of the many fruitless abdominal operations done because of symptoms due to ureteral stricture, that for supposed appendicitis heads the list. If one simply keeps in mind the usual location of the appendix near the anterior superior iliac spine, and the location of the ureter near the umbilical region, this mistake will not occur so frequently in the future. The ureter, at the pelvic brim crossing, lies over the anterior portion of the sacroiliac joint and one may have difficulty in differentiating by palpation a tender ureter from an arthritis, but we gain additional knowledge by palpation of the joint posteriorly and especially by palpation of the ureter in its juxtavesical portion.

In attempting to differentiate an obscure abdominal complaint by the aid of palpation, one must not lose sight of the fact that ureteritis is of such common incidence that it frequently occurs in association with the various other abdominal and pelvic diseases; and it is the duty of the diagnostician to evaluate the various obscure signs and symptoms and to advise the patient as to the sequence of the proposed lines of treatment.

I have briefly outlined a few of the outstanding features one should bear in mind in attempting to place a helpful diagnostic label on

some of the patients heretofore directed to the wrong specialist or nursed by the general practitioner as neurasthenics. In patients complaining of obscure symptoms referable to a possible lesion in the back, abdomen, or pelvis, an open ear should be kept for any complaint of bladder trouble, an open eye for any suggestion of pathologic findings in the urine, and inquisitive finger tips for any signs of soreness or tenderness along the urinary tract.

Time forbids a full discussion of the many interesting points in differential diagnosis. There is probably no other local disease which gives rise to such protean symptoms as does ureteral stricture. Many of its more general manifestations result, of course, from its effects on the upper urinary tract. Because of its usual location in the pelvis its local discomforts are most often charged to the internal genitalia. From the involvement of the neighboring nerves, we have referred symptoms upward to the flanks, posteriorly to the sacral and sciatic regions, laterally to the hips, and downward to the groin, thighs, legs, and even to the toes. The downward radiations within the pelvis give rise to annoying bladder, uterine and rectal symptoms, and the pains referred to the vagina and perineal regions often lead to misdirected operations.

As a result of the urinary stasis we have all grades of damage to the kidneys, with the resultant local and referred renal pains, and widespread general symptoms such as headache, fever, malaise, thoracic pain, and gastrointestinal symptoms.

The internists who have given attention to this disease report to me their amazement at the number of chronic gastrointestinal complaints which are traceable to defective urinary drainage, and at the satisfactory results obtained from treatment. I cannot emphasize this point better than by quoting from a table in a previous publication¹:

TABLE I.—ASSOCIATED SYMPTOMS IN URETERAL STRICTURE.

Complaint.	Number of patients.	Relief, partial or, total.	Percentage.
Indigestion	24	17	71
Anorexia	26	20	77
Nausea	56	25	45
Gas	42	26	62
Diarrhea	15	9	60
Rectal pain or pressure	28	19	68
Mucous colitis	15	12	80

Our title calls for a discussion of the pathology and treatment of ureteral stricture, but our space is limited. Those interested in the pathology are referred to a recent publication by Hunner and Wharton,² also to the publication by Goldstein and Carson³. The chief interest from the pathological viewpoint lies not in a study of the simple inflammatory stricture area of the ureteral wall, but

in a study of the many renal lesions resulting from the stasis of urine caused by the ureteral disease. The more common renal diseases which in large measure may be traced back to the injury caused by ureteral stricture are hydronephrosis (sterile or infected), chronic pyelitis and pyonephrosis, pyelitis of the pregnant and puerperal periods, chronic pyelitis in children, renal and ureteral calculi, the renal inflammatory processes resulting in the so-called essential hematurias, and the various pathological processes which drive to the urologist the patient with congenital malformation of the upper tract. It is probable that many of the chronic nephritides resulting in multiple abortions are secondary to stricture, as are some of the chronic renal processes formerly considered as amenable only to medical methods of treatment.

Inasmuch as the renal injury in the above list of pathological processes arises largely from defective drainage it is a mere truism to state that the first requirement of intelligent treatment is *the establishment of good drainage*. Focal infections are not only responsible for most ureteral strictures, but they sometimes contribute factors of direct injury to the renal substance, thereby furnishing two urgent reasons for the early discovery and eradication of possible foci of infection as one of the primary requisites of treatment in dealing with many of the above renal diseases.

Conclusions. Ureteral stricture is one of the most common lesions of the abdominopelvic cavity. The symptoms due to its presence are most protean in character and lead to more errors in diagnosis and to more ill-directed therapeutics and unnecessary operations than those of any other disease.

The attendant anamnesis and physical findings are such that the general practitioner, if he but have the disease in mind, can usually make the diagnosis with even more certainty than obtains in dealing with cases of chronic appendicitis or chronic cholecystitis.

The chief interest to the pathologist centers in a study of the renal lesions caused by the presence of ureteral stricture.

The treatment is usually nonsurgical and consists in relief of the local symptoms and improvement in the kidney function, by dilatation of the stricture area and restoration of adequate renal drainage. Clinical experience seems to point to distant foci of infection as the most frequent cause of ureteral stricture, and treatment often fails to give permanent relief until the original focus of infection is eradicated.

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DOUBLE TACHYCARDIA.

COEXISTENT AURICULAR AND VENTRICULAR TACHYCARDIA DUE TO DIGITALIS.

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SINCE the return to the use of larger doses of digitalis, for which the careful studies of Eggleston are so much responsible, the usefulness of this drug has been many times enhanced. The popularity of the larger doses, however, has resulted in a very much better opportunity for observing its toxic effects. The danger of overdosage is a very real one, and it is well to be familiar with its toxic manifestations. The occurrence of $A-V$ block as a result of digitalis has long been familiar, and was emphasized by Christian¹ in 1915, who reported a series of cases showing such a block with varying ventricular complexes, but not exhibiting tachycardia. In 1918 Vaughan,² in reporting 2 cases of ventricular tachycardia, suggested that such a phenomenon might be caused by digitalis, although in his cases this did not seem to be the case. Schwensen,³ in 1922, reported 2 cases of ventricular tachycardia which were thought to be due to digitalis, and the same year Danielopolu⁴ reported 3 cases of paroxysmal tachycardia due to digitalis or strophanthus. These had been observed as early as 1911 and 1913, and the polygraphic tracings which accompany the report leave one in some doubt as to the origin of the tachycardia.

In 1923, Felberbaum⁵ reported a case very similar to Schwensen's, and the following year Reid⁶ reported 3 cases of ventricular tachycardia due to digitalis. The tracings in the first of his 3 cases seem to show an independent auricular action with $A-V$ block.

Luten's⁷ studies, published in 1925, include the records of 4 patients with normal cardiac mechanism, in whom large doses of digitalis provoked auricular tachycardia with $A-V$ dissociation and independent ventricular rates varying from 90 to 162. Luten drew a parallel between these clinical manifestations, and "the events that occur when the heart of a cat is progressively poisoned by digitalis," as shown by Robinson and Wilson: "First inversion of the T wave of the electrocardiogram occurred. After additional amounts of the drug were administered depression of the atrioventricular conduction made its appearance. At about this time there was some slowing of the heart rate, which came on gradually. After still larger amounts there was an increase in the rhythmicity of the auricles and of the ventricles (producing acceleration of both). The ventricular rate soon exceeded that of the auricles thus producing atrioventricular dissociation. At about this stage

idioventricular complexes made their appearance. Independent ventricular rhythm, with abnormal ventricular complexes, developed. This was soon followed by ventricular fibrillation and death."

Another paper of Luten's⁷ adds 3 more cases of tachycardia due to digitalis, 1 showing a coexistent auricular and ventricular tachycardia and 2 showing ventricular tachycardia associated with auricular fibrillation. This paper discusses a peculiar type of tachycardia in which alternating types of ventricular complexes occur, corresponding to the cases reported by Schwensen, Felberbaum and one of Reid's cases.

Several of the authors quoted point out the danger of mistaking the rapid, regular, cardiac action of ventricular tachycardia due to digitalis for an auricular flutter, for which more digitalis would be indicated.

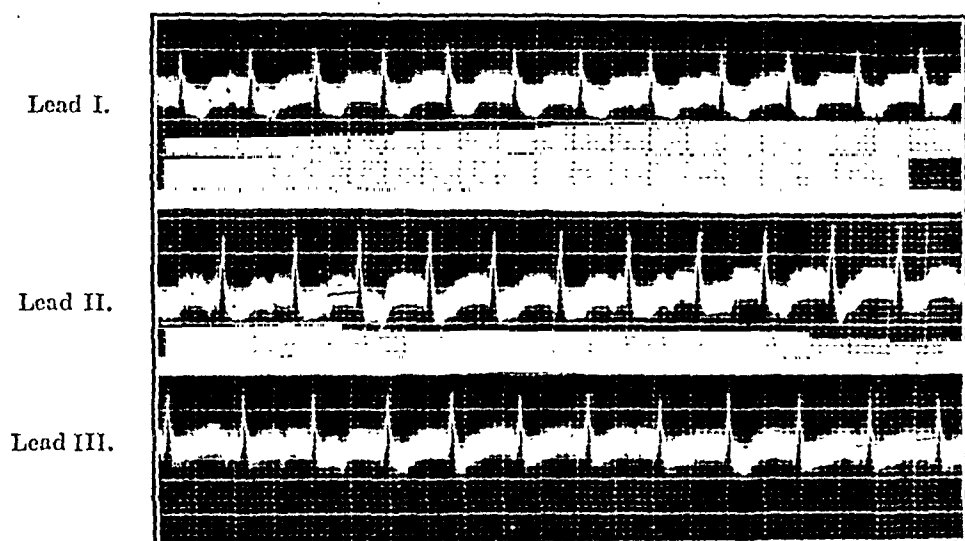
The following case is reported as another instance of the peculiar double tachycardia sometimes caused by digitalis:

Mrs. D. entered the Long Island College Hospital on May 29, on the obstetrical service of Dr. John O. Polak, complaining of orthopnea and weakness. She was eight months pregnant.

She had measles in infancy and rheumatic fever at the age of eight years. At fifteen years she began to notice shortness of breath on exertion, but suffered no serious break in compensation until the present illness. She became pregnant for the first time eight months before admission, and went through the early months of pregnancy without nausea, edema or headache. Four weeks before admission she became very short of breath, and from that time on was incapacitated, dividing her time between the bed and sitting up in a chair. She first noticed edema two weeks before admission and this grew progressively worse. For twenty days before admission she was said to have received 20 minims of digitalis, three times a day, and in the last twenty-four hours was given three doses of strophanthin, gr. $\frac{1}{100}$, hypodermically. The digitalis may have been given as drops rather than minims, which would materially lessen the dose but the total must have been between 40 and 80 cc. She had also been given several doses of morphin for periods of depression, described as sinking spells.

On admission her temperature was 99; pulse, 130; respiration, 28. She was very cyanotic and unable to lie down. She was bled 250 cc. and was given caffein and morphin. The following day she began to vomit and this continued until her death, two days later.

At noon on May 31 the following notes were made: "Pale, little woman propped up in bed, showing moderate cyanosis and a mild degree of dropsy over her sacral region and in the legs. Moist rales at both bases. The heart is enlarged, and presents the typical signs of double mitral disease. The pulse is 168 and is quite



Double tachycardia due to digitalis. Regular inverted *P* waves occurring at the rate of 195. Complete block. Regular ventricular waves of normal contour occurring at the rate of 160.

regular except for recurring waves of somewhat more rapid action, which appear to be of sinus origin. The abdomen shows pregnancy at about the eighth month."

An electrocardiogram was taken an hour later by Dr. C. M. Anderson. Her pulse continued to be very rapid. She grew weaker and more dyspneic, complaining of pain at times in the precordial region. At 9.30 she died. No autopsy was permitted.

The electrocardiogram shows a regular series of inverted *P* waves occurring at the rate of 195. This represents an auricular tachycardia originating in an ectopic focus in the auricle. There is a complete *A-V* block and a perfectly regular series of ventricular beats occurring at the rate of 160 and showing a normal "supraventricular" form. The ventricular tachycardia evidently originates in a focus lying between the *A-V* node and the bifurcation of the bundle.

This combination of auricular tachycardia, *A-V* dissociation, and ventricular tachycardia seems to be a characteristic digitalis effect. Search was made among the published records for similar curves. Gallavardin⁸ described such a case in 1920, making no mention of whether or not any drugs of this class had been administered. In the second of Robinson and Herrmann's⁹ 4 cases of ventricular tachycardia this combination was noted. This patient probably had a coronary thrombosis, and had been given one dose of strophanthus. The first of the 4 cases of ventricular tachycardia reported by Wolferth and McMillan¹⁰ showed an independent auricular tachycardia, but no mention is made of digitalis. After the paroxysm had subsided a bigeminy was noted. Barker¹¹ noted periods of ventricular tachycardia during the course of a paroxysm of auricular tachycardia, but no mention is made of digitalis. The same is true of the case reported by Porter,¹² in which the ventricular tachycardia lasted one hundred and fifty-three hours. The curves in this case show *A-V* dissociation with a coexisting auricular tachycardia.

Summary.—1. A brief review of some of the toxic effects of digitalis is presented.

2. Another case is reported in which there was observed auricular tachycardia, *A-V* dissociation and ventricular tachycardia following the administration of large doses of digitalis.

3. Eleven other cases of double tachycardia are collected from the literature. Six of these are known to have received large doses of digitalis. One received but one dose of strophanthin and was probably suffering from coronary thrombosis. The other five may or may not have received drugs of the digitalis class.

Conclusion.—1. The occurrence of *A-V* dissociation with independent auricular and ventricular tachycardia should arouse the suspicion of overdosage with digitalis.

2. The occurrence of a rapid regular pulse following the administration of drugs of the digitalis class should be studied by the electrocardiograph before proceeding further with digitalis administration.

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SICKLE-CELL ANEMIA; REPORT OF TWO CASES FROM OHIO ILLUSTRATING ITS HEMOLYTIC NATURE.

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ATTENTION was first called to sickle-cell anemia by Herrick¹ of Chicago, in 1910 when he reported the occurrence of "sickle and bizarre-shaped erythrocytes" in the circulating blood of an East Indian negro. The condition was detected in a routine examination of the blood, and the negro had had no symptoms referable to his anemia. Since this time, there have been reports of 105 cases occurring in different parts of the United States. All these cases have similar symptoms and physical signs and a characteristic blood picture. There have been no reported cases occurring in the white races. Sydenstricker² has studied 80 distinct cases and concludes, as does Huck³ in his studies of 17 cases, that the condition is a familial and hereditary disease of negroes occurring indiscrimi-

nately in both sexes, characterized by the presence of peculiar sickle-shaped erythrocytes in the blood stream, a moderately severe anemia, a varying degree of jaundice, physical and sexual underdevelopment, a general glandular enlargement and, in most cases, ulcer of the legs. Emmel⁴ has shown that there are two forms of the disease: (1) Those cases in whom the sickle cells are actually in the circulating blood (the "active sickler"); (2) those in whom the cells become sickle-shaped after standing in a closed chamber for a number of hours (the "latent sickler"). There are all gradations between these types, depending on the severity of the disease.

There have been five necropsies reported on patients with active sickle-cell anemia and the following pathologic conditions were found:

1. A peculiar type of poikilocytosis.
2. A profound anemia.
3. A small, contracted, fibrotic spleen with large numbers of old and recent hemorrhages and evidence of increased blood destruction in and about the Malpighian corpuscles.
4. A bone marrow showing a marked diminution in fat with a large number of sickle- and bizarre-shaped red blood cells, and a rather marked hyperplasia in some cases.

Cases have been reported in various parts of the United States. Two cases have been reported from the midwest and the remaining cases have been reported from Baltimore and in the South.

The following cases are of interest, since they are the first two that have been reported in this locality. They agree in every particular with the cases that have been reported and show the familial incidence of the disease. They show very plainly the many points of similarity of the disease to hemolytic jaundice and how the physical signs may lead one to an erroneous diagnosis of congenital or tertiary syphilis and even an acute appendicitis.

It is through the courtesy of Dr. Roger S. Morris and Dr. A. Graeme Mitchell, on whose services these cases appeared, that I am permitted to make this report.

Case Reports. CASE I.—(Hosp. No. K-3203.) U. H., a negro schoolboy, aged eighteen years, was admitted to the surgical service of the Cincinnati General Hospital, April 22, 1925, with a diagnosis of chronic leg ulcers, probably due to syphilis. His chief complaint was sores on the legs.

Family History. The mother living and well. The father died of a "blood disease," having had ulcers of the legs before death. Two sisters died in infancy. One brother is living and well.

Past History. The patient has always been frail, never able to take part in play with his fellows; he has been under weight and has been troubled with shortness of breath. The patient was born in Georgia, where he lived most of his life. He had pneumonia,

measles and mumps in childhood. He has been unable to play or work to any extent in the past eight years because of leg ulcers. He has suffered at various times with acute epigastric pain and nausea. This soon passed off and he thought nothing of it. He has had no cardiovascular complaints other than his dyspnea on exertion and occasional palpitation. There have been no genito-urinary complaints. He has always had more or less of a greenish-yellow color to his eyes.

Present Illness. The onset was eight years ago, following an abrasion of the left leg which soon enlarged and became an ulcer and persisted in spite of all treatment. An abrasion to the left ankle was soon followed by a similar ulcer.

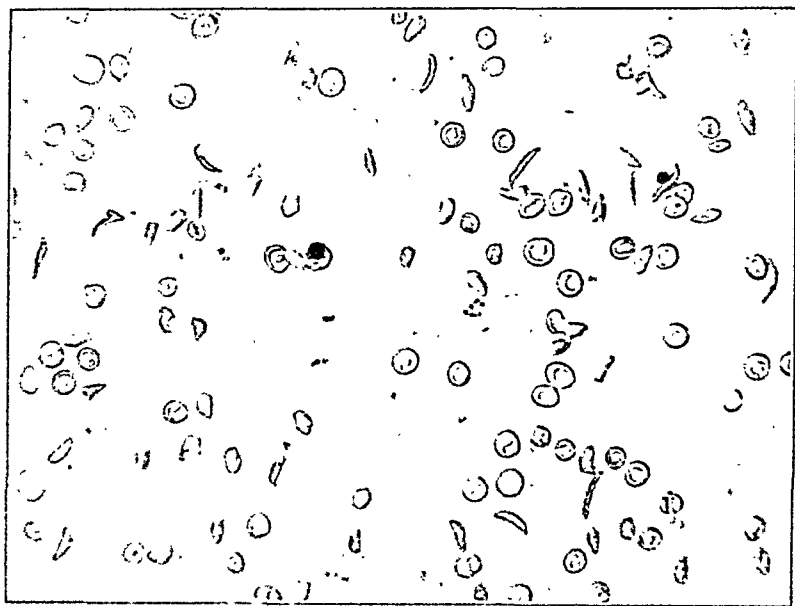


FIG. 1.—Case I. Stained blood smear.

Physical Examination. The patient is a very much under-developed negro male of eighteen years, appearing to be about twelve or fourteen years. He is well nourished, however; he does not appear acutely ill. There is a flaring of the lower costal borders with a distended abdomen. There is no pubic or axillary hair. The pulse is of low tension and somewhat frequent; the blood pressure is 98/50. There is a general adenopathy, the glands being hard and shotty. The sclerae show a greenish-yellow color. The pupils are normal. The tongue is pale and moist. There is slight decay of the teeth. The tonsils are small and cryptic. The chest is fairly well developed and symmetrical. Expansion is limited, but equal. The lungs are clear to palpation, percussion and

auscultation. The heart apex is in the fifth space, 10 cm. from the midsternal line. Cardiac dullness extends $11\frac{1}{4}$ cm. to the left, 4.5 cm. to the right in the fourth space. The heart sounds are of fair quality and there is a systolic murmur at the apex, propagated to the left axilla. There is also a systolic murmur at the base, heard best at the pulmonic area. The abdomen is distended, being above the level of the chest, making examination difficult. The liver edge is palpated about 3 cm. below the right costal margin and is slightly tender; the surface seems smooth. The spleen is not palpable. The genitalia are infantile. The muscles of the arms and legs are poorly developed, especially the legs. There is a large superficial ulcer on the anterior aspect of the middle of the left leg, oval in outline, with the long axis parallel to that of the tibia. The edge is rather sharply outlined, slightly undermined, surrounded by deeply pigmented skin which overlies rather dense scar tissue. The base is dirty and covered with unhealthy granulations. Just above the right ankle on the outer side is a similar, though smaller ulcer. The reflexes are normal. Rectal and ophthalmoscopic examinations are normal.

Laboratory Examinations. The white blood cells varied from 15,400 to 9000 and the red blood cells from 1,600,000 to 2,200,000 on discharge; the hemoglobin from 45 to 50 per cent. Differential count showed 23 per cent lymphocytes; 2 per cent large mononuclears and transitionals; 68 per cent polymorphonuclear neutrophils, 2 per cent eosinophils and 2 per cent basophils. There was marked; poikilocytosis and anisocytosis; there was 10 per cent of sickle cells. On allowing a sealed wet smear to stand twenty-four hours, there was a very marked increase in the number of sickle cells. Fragility of the red blood cells in hypotonic salt solution was normal. The van den Bergh reaction showed hyperbilirubinemia. The urine was normal, except for a slight increase in urobilin. The gastric contents after an Ewald test meal showed 16 free hydrochloric acid and 43 total acidity. Stool examination on three occasions was normal. Blood Wassermann on three occasions was negative. Roentgen ray examinations of the chest and of the tibiae were negative.

During the stay in the hospital the patient's temperature fluctuated from normal to 101° F., seldom remaining normal for a whole day at a time. He showed very little reaction to treatment.

Splenectomy was advised, but patient refused to have operation.

The immediate family of the patient were examined. His mother, aged forty years, had no symptoms. Physical examination was essentially negative, except for a slight greenish tinge to the sclerae. The red blood cells were 4,800,000 and white blood cells 6000. The urine was negative. There was a very marked latent sickling of the red blood cells. The brother was normal physically and showed no active or latent sickling of the red blood cells.

CASE II.—(Hosp. No. K-7679.) A. L., a negro boy, aged four years, was first admitted to the Cincinnati General Hospital January 16, 1922, at the age of fourteen months. He was discharged two days later with a diagnosis of rickets and otitis media. The physical examination except for the otitis media and signs of rickets was negative and no note was made of any abnormality in the red blood cells. The blood at this time showed 44,200 white cells, of which 31 per cent were polymorphonuclear leukocytes, 67 per cent lymphocytes, 2 per cent transitional cells.

The patient was admitted the second time in November of 1923 on the contagious service with scarlet fever; was discharged as well, after two months. No abnormality in the blood was noted at this time.

The patient was again admitted on September 22, 1924, complaining of abdominal pain and constipation.

Family History. The mother was living and well; the father was living, but his whereabouts were unknown; two other children were living and well; two children dead, one at eight months, cause unknown, one at fourteen months of chronic bowel trouble. There was no history of miscarriages.

Past History. The patient was a full-term baby with normal delivery, breast-fed for three months, but has always been in poor health. He had had measles, mumps, chicken pox, whooping cough and scarlet fever. The tonsils and adenoids were removed following recovery from the latter.

Present Illness. On the day of admission he had been taken acutely ill with a fever and pain in the abdomen, without any vomiting. He had been constipated for two days.

Physical Examination. The patient is an underdeveloped but fairly well-nourished negro child of three years. His mental capabilities do not seem to have advanced with his age. The abdomen is distended and the costal borders flare. The sclerae have a greenish-yellow tinge. Pupils are normal. The teeth have a chalky appearance. The tonsils are not seen. Respirations are rapid and quick. There is slightly impaired resonance at the base of the right lung but no rales. The cardiac borders are slightly enlarged to the right and a systolic murmur, transmitted equally in all directions, is heard. The abdomen is distended. The liver edge is felt 6 cm. below the costal margin. It is smooth and soft. The spleen is just palpable under the costal margin. There is a slight generalized tenderness of the abdomen.

Laboratory Examinations. The urine was normal. The blood showed 3,200,000 red blood cells; 60 per cent hemoglobin and 14,000 white blood cells. Differential count revealed 71 per cent polymorphonuclear neutrophils; 11 per cent lymphocytes; 18 per cent large mononuclears and transitionals and a large number of normoblasts. Opinion as to the diagnosis at this time was divided between

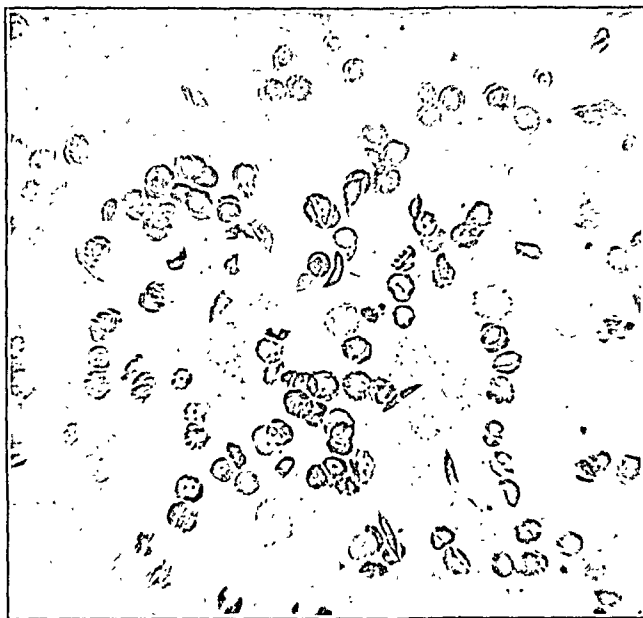


FIG. 2.—Case II. Fresh blood.

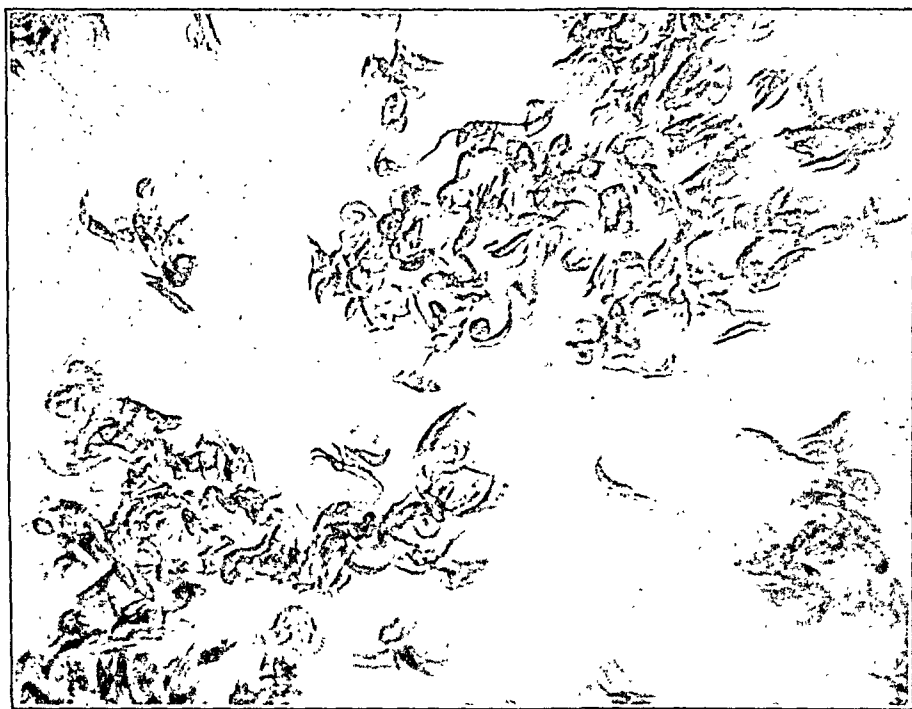


FIG. 3.—Case II. Blood after standing thirty-six hours.

a beginning pneumonia and an acute appendicitis. The acute process subsided, however, without operation.

Course in Hospital. During stay in the hospital the temperature remained essentially within the normal range after the first few days. Repeated examinations of the blood showed an average of 60 per cent hemoglobin; white blood cells to range between 20,000 and 14,000; red blood cells between 3,200,000 and 3,750,000. The differential count showed some variations, the polymorphonuclear neutrophils ranging between 70 and 49 per cent; lymphocytes between 50 and 22 per cent. Normoblasts ranged from 67 per 100 red blood cells to 4 per 100 red blood cells. The platelet count was normal. The van den Bergh reaction showed a hyperbilirubinemia. Roentgen ray of the chest and gastroenteric tract was negative. The Wassermann reaction was negative.

The child's general condition improved gradually, the spleen remained palpable just below the costal margin, the liver decreased somewhat in size. The discoloration of the sclerae remained essentially the same. The patient was discharged December 24 (two months after admission) with no definite diagnosis, but appearing in fairly good condition.

The patient was admitted on October 6, 1925, to the surgical service following a fall in which he suffered injury to the head and right arm. He had been well following the previous admission except for an occasional cold. A diagnosis of acute osteomyelitis was made and the patient was operated on but no pathologic process was found and recovery was uneventful. Physical examination at this time showed practically the same signs as on last admission, the greenish-yellow sclerae, a palpable liver and spleen and the same heart signs. Blood on admission showed 32,000 white blood cells; 60 per cent hemoglobin and 3,500,000 red blood cells; a differential count consisting of 30 per cent polymorphonuclear neutrophils; 19 per cent lymphocytes and 3.7 per cent transitionals. There was a slight anisocytosis and poikilocytosis. The platelets seemed normal. There were 44 normoblasts to every 100 white blood cells counted. There were 1 to 3 sickle-shaped cells per 100 red blood cells. On allowing a sealed wet smear to stand twenty-four hours there was a marked increase in the number of sickle cells. The van den Bergh reaction suggested increased bilirubinemia of hemolytic origin, but less marked than on the previous admission. Fragility of the red blood cells was normal. The urine was normal except for a slight increase in the urobilin content. The patient improved slightly under rest and iron tonics but an acceptable donor for transfusion could not be obtained and splenectomy was thought inadvisable because of the anemia. Patient was discharged on December 14 as improved, with a diagnosis of sickle-cell anemia.

The mother of this patient was examined. She had no symptoms. She was undernourished and underdeveloped. Physical examination was essentially negative except for a slight greenish tinge to the scleræ. Red blood cells were 3,800,000; white blood cells were 7000. There was a marked latent sickling of the red blood cells. Urinalysis was negative.

Comment. Case I shows plainly how the sickle-cell anemia may be confused with tertiary syphilis. For three months the patient's leg ulcers were considered syphilitic in origin. In Case II the pain in the abdomen and distention coming on suddenly was in all probability due to a splenic hemorrhage, yet it was thought to be an acute appendicitis at the time.

The treatment of sickle-cell anemia is very unsatisfactory. The general supportive measures, overfeeding, iron, and with rest in bed give only temporary relief. The good from transfusion is only short-lived. Splenectomy has been suggested but never attempted. In view of the fact that the disease is so similar to hemolytic jaundice, in which splenectomy is curative, and that all or most of the red-cell destruction apparently takes place in the spleen, it seems that splenectomy should be tried. The prognosis is bad. The course of the disease is gradually a downward one, the patients rarely living beyond thirty years of age.

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ESSENTIAL HEMATURIA AND ITS POSSIBLE RELATIONSHIP TO PURPURA HEMORRHAGICA.

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WHEN a careful cystoscopic examination demonstrates hemorrhagic urine coming from one or both kidneys which give normal functional tests, and the pyelograms are negative, a diagnosis of essential hematuria is warranted. To assert that such a diagnosis means that an early neoplasm, nonopaque calculi or an obscure infection has been overlooked would seem to discredit the perfection of modern urologic technique or the capability of the examiner. That such oversights are the exception rather than the rule is the experience of every urologist who has followed a series of cases of essential hematuria over a period of years. Neoplasm does not eventuate nor are stones passed, nor does tuberculosis or other infection usually appear. Good health is usually maintained and recurrence seldom follows proper treatment.

It is unfortunate that a diagnosis of essential hematuria should be interpreted by some as evidence that a gross lesion of the urinary tract surely has been overlooked; it is as deplorable as it is inevitable that this desire to limit the etiology of this disease to a narrow field should tend to discourage search for some more remote and more obscure cause.

Several years ago Quinby¹ studied 2 cases of essential hematuria in which nephrectomy had been performed. He found that the hemorrhage was from the pelvis and the tips of the pyramids. In each instance hemorrhage occurred within the peripelvic tissues, often appearing just beneath the epithelium, where, for considerable distances, the epithelium had been elevated by a layer of extravasated blood. In 1 case there was no evidence of inflammatory reaction in the tissues of the pelvis or around the bloodvessels. The hemorrhages were represented by extravasations of red blood cells from thin-walled dilated capillaries and veins. Just beneath the epithelium of the pelvis unruptured, large, thin-walled vascular channels were seen, evidently considerably distended. Even larger arteries showed extravasated blood external to the adventitia. The vascular channels between the collecting tubules of the pyramids, especially those nearer the apex, were very wide, often irregular and tortuous, giving the appearance of vascular sinuses rather than of veins or capillaries. These sinuses were distended with blood. Although no organisms could be demonstrated in either

case, in the second there was more suggestion of an infectious cause, there being a distinct inflammatory reaction and evidence of vascular injury.

Believing from these findings that an obscure focus might be the cause of these localized lesions in the kidney, we injected a considerable number of laboratory animals with cultures from foci of infection in 9 patients having essential hematuria. In none of these animals could we demonstrate any renal lesions, although Meisser, with whom we were carrying on this laboratory study, was finding positive results in more than 80 per cent of animals similarly injected with cultures from patients suffering with pyelonephritis and elusive ulcer of the bladder of Hunner.

Because of the fact that bleeding elsewhere, especially from the nose, skin, mucous membrane of gums and mouth, or in the subcutaneous tissues, alone or in combination, is seen as a result of a deficiency of some blood element necessary to the maintenance of the blood in the vessels, it seemed possible that some deficiency of elements necessary for the coagulation of blood might explain certain cases of essential hematuria.

Instances of hematuria are not unusual in cases of purpura of various forms and cases of hemophilia. Cases of purpura of the urinary tract, with cystoscopic finding of purpuric areas in the bladder, without hemorrhage elsewhere, have been described by Blum² and Praetorius.³ Yet we find no suggestion in the literature that cases of bleeding from the kidney for long periods or at long intervals may be due to a deficiency in some of the coagulation elements of the blood. The possibility that such might be the case with essential hematuria was enhanced by the observation by one of us (Conner) of several cases of menorrhagia without local explanation, which we believed to be due to a deficiency in coagulation factors. It is possible that some cases of local hemorrhage elsewhere, in the stomach, intestine, eye and so forth, may be explained on the same grounds.

If, besides a deficiency in some of the coagulation factors, there is a local predisposing cause, such as unusual vascularity of the mucous membrane or an area of localized infection, the possibility of bleeding is greatly increased. That lavage of the renal pelvis with a styptic solution, such as silver nitrate, will frequently stop such bleeding would suggest such a localized cause.

In searching for some factor concerned in the coagulation mechanism of the blood we paid particular attention to the blood platelets, coagulation time and bleeding time. The calcium coagulation time and the prothrombin time were also estimated in nearly all cases, and the possibility of bleeding elsewhere was carefully investigated.

Thirty-three unselected cases were observed. Most of them were seen between December, 1923, and September, 1925. In 22 the diagnosis of essential hematuria was unquestioned; in 11

others a diagnosis of probable essential hematuria was made. A study was made of age, sex, lapse of time since the first appearance of hematuria, family history of bleeding, and personal history of bleeding from the gums, epistaxis, hemoptysis, hematemesis, melena, menorrhagia, purpuric spots and "easy bruising." At the examination particular attention was paid to the presence of petechiae, purpuric spots, hemorrhagic areas of the gums and mouth, to the tourniquet test and palpability of the spleen.

Cases of Essential Hematuria (Table I). The oldest of the 22 patients was sixty-seven years and the youngest nineteen years; the average age was forty-two and a half years. There were 15 males and 7 females. The duration of the symptoms was from two days to twenty years; in 1 case the duration was not recorded, and the average duration for the other 21 cases was five years and forty-one weeks. There was a history in 5 cases of other members of the family having suffered from hemorrhage, no such history in 11 and no record in 6. The mother had had epistaxis in 1 case, the father intestinal hemorrhage in 1, a brother hematuria in 1, the mother hemoptysis in 1 and a son epistaxis in 1. Personal history of bleeding from the gums was positive in 2 cases, negative in 16 cases and there was no record in 4. Epistaxis had occurred in 5 cases, in 14 it had not and in 3 there was no record. There was no history of hemoptysis in 18 cases and there was no record in 4. In 19 cases hematemesis had not occurred, and there was no statement regarding it in 3. In 19 cases melena was not admitted and there was no record in 3. In 2 of the 7 female cases menorrhagia had occurred; in 5 it had not. In 18 cases the existence of purpuric areas was denied; in 1 the patient stated that they had occurred, and there was no statement regarding it in 3 cases. There was a history of "easy bruising" with resultant "black-and-blue" areas in 2 cases; it had not occurred in 14 cases and in 6 there was no record. There was a history of gross hematuria in all but 1 case.

On examination there were no petechial areas nor purpuric spots noted, and no hemorrhagic areas elsewhere. The tourniquet test was rated in 1 case as Grade 1—, on a scale of 1 to 4; in 5 cases as Grade 1, in 2 as Grade 1+, in 3 as Grade 2, in 1 simply positive and in 7 negative. In 3 cases no statement was recorded.* The spleen was not felt in any instance; there was a specific note of inability to palpate the spleen in 7 cases and no specific mention made of the spleen in the other cases.

* The tourniquet test is made by applying the arm band of the sphygmomanometer above the elbow for exactly three minutes at a pressure midway between the systolic and the diastolic pressures, usually about 160. The appearance of petechial areas below the band is interpreted as a positive test. This test is one of importance in the diagnosis of purpura hemorrhagica. The extent and intensity of the subcutaneous hemorrhage indicate the degree of positiveness of the test.

The number of erythrocytes varied from 3,720,000 to 4,990,000 per c.mm., the average being 4,344,000. The hemoglobin varied from 60 to 88 per cent, and averaged 72 per cent; it was measured with the Dare instrument, which is somewhat too low in the higher readings. The number of leukocytes varied from 4600 to 12,000 per c.mm., averaging 7800. The platelet count varied from 74,000 to 272,000 per c.mm., averaging 141,000; the lowest average platelet count for the individual patient was 96,000 and the highest 202,000, the normal platelet count being between 200,000 and 250,000. In 1 case the platelets averaged below 100,000; in 5 cases, from 100,000 to 125,000; in 6 cases, between 125,000 and 150,000; in 8 cases between 150,000 and 175,000; in 2 cases, more than 200,000. In 6 cases one count was below 100,000; in 2 cases two or more counts were below 100,000. It is interesting that in all except 1 case in which any degree of positiveness of the tourniquet test was shown the platelet count was more or less lowered. Conversely, in most cases in which a lowered platelet count was shown there was some degree of positiveness of the tourniquet test. The coagulation time by the Boggs method varied from three to eight and a half minutes, averaging five and three-tenths minutes. The normal time is from three to five minutes. The bleeding time varied from one to three and a half minutes, with an average of one and four-fifths minutes. The normal bleeding time is from one to one and a half minutes. The coagulation time by the Lee method varied from five and a half to sixteen minutes, averaging nine and two-fifths minutes. The normal time is from eight to eleven minutes. In no case was there sufficient change in the coagulation time by the addition of calcium to justify the assumption that there was a deficiency of calcium in the blood. In no case was the prothrombin time sufficiently prolonged to justify the assumption that there was a deficiency of prothrombin in the blood. In 1 case the prothrombin time on one examination was sixteen minutes with the optimal amount of calcium, but on another examination the time was twelve minutes; in 1 case the prothrombin time was twenty-six minutes on one examination and later only eleven minutes. In both of these second tests the results were within normal limits. The clot-retraction time was normal in all except 1 of the 6 cases in which the test was done; in this 1 case retraction was complete in two hours instead of one hour, as is normal. The Wassermann reaction was negative in the 18 cases in which the test was made. There was gross hematuria at the time of examination in 9 cases, and no hematuria at the time of examination in 2 cases. Infection of the teeth was present in 5 cases as Grade 1, in 5 cases as Grade 2 and in 2 cases as Grade 3. There was evidence of chronic tonsillitis in 9 cases, and the tonsils had already been removed in 3 cases; no mention was made of the tonsils in 5 cases.

TABLE I.—ESSENTIAL HEMATURIA.

Case	Age, sex and sex.	Duration of illness	History.										Examination.																				
			Family history of bleeding.	History of bleeding gums.	Epistaxis	Menorrhagia	Hemoptysis	Hematemesis	Melena	History of gross hematuria.	Purpura.	Easily bruised.	Petechiae.	Purpuric spots.	Hemorrhagic areas elsewhere.	Tourniquet test, grade.	Palpable spleen.	Erythrocytes, millions per cmm.	Hemoglobin, per cent.	Leucocytes, thousands per cmm.	Platelet counts, thousands per cmm.	Average platelet count, thousands per cmm.	Coagulation time (Boggs), minutes.	Coagulation time (Lee), minutes.	Bleeding time, minutes.	Calcium time, minutes.	Prothrombin time with optimal calcium, minutes.	Clot retraction in one hour.	Hours in which clot retraction is complete.	Wassermann reaction.	Teeth, periapical infection.	Tonsillitis.	Hematuria, grade.
1	15	8 yrs.	1	0	0	0	0	0	0	0	0	0	0	0	1	1	4.63	71	8.0	122	127	4.5	9.0	2.0	9.0	10	0	2.0	0	0	0	+	0
2	35	5 yrs.	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1.59	70	7.5	180	149	5.0	16.0	1.5	11.0	10	1	1	0	0	0	+	5
3	51	3 wks.	0	1	1	1	0	0	0	1	1	0	0	0	0	0	4.36	70	5.0	162	137	7.3	13.0	3.0	10.0	10	1	1	0	0	0	+	3
4	40	20 yrs.	0	0	0	1	1	0	0	0	0	0	0	0	0	1	4.26	70	6.8	130	134	4.0	9.5	2.0	9.5	10	1	1	0	0	0	+	3
5	35	20 yrs.	1	1	0	0	0	0	0	0	0	0	0	0	0	1	4.46	71	7.6	138	169	4.0	7.0	3.5	11.0	10	1	1	0	0	0	+	3
6	52	12 yrs.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3.80	65	6.5	182	100	5.5	7.0	1.5	11.0	12	1	1	0	0	0	+	3
7	39	17 yrs.	0	1	0	0	0	0	0	1	0	0	0	0	1	1	4.31	71	4.6	80	100	4.5	6.5	1.5	4.5	10	1	1	0	0	0	+	3
8	42	1 yr.	0	1	0	0	0	0	0	1	0	0	0	0	1	1	1.57	72	9.2	106	100	8.5	12.0	0.5	20.0	11	1	1	0	0	0	+	4
9	26	3 mos.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4.21	70	7.3	192	162	7.5	7.0	2.0	8.5	26	1	1	0	0	0	+	4
10	26	3 mos.	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1.18	80	11.0	272	162	4.0	12.0	3.5	15.0	11	1	1	0	0	0	+	4
			Mother, taxin														4.37	71	7.6	146	162	4.0	8.0	3.0	0.0	0.0	13	1	1	0	0	+	5

TABLE II.—POSSIBLE ESSENTIAL HEMATURIA.

History.			Examination.																				Pyorrhea.												
Case.	Age, sex, and race.	Duration of illness.	Family history of bleeding.	History of bleeding gums.	Epiptaxis.	Mecorrhagia.	Hemoptysis.	Hematuria.	Melena.	History of gross hematuria.	Purpura.	Easily bruised.	Petechiae.	Purpuric spots.	Hemorrhagic areas elsewhere.	Tourniquet test, grade.	Palpable spleen.	Erythrocytes, millions per c.mm.	Hemoglobin, per cent.	Leukocytes, thousands per c.mm.	Platelet counts, thousands per c.mm.	Average platelet count, thousands per c.mm.	Congulation time (Boggs), minutes.	Congulation time (Lee), minutes.	Bleeding time, minutes.	Calcium time, minutes.	Prothrombin time with optimal calcium, minutes.	Clot retraction in one hour.	Hours in which clot retraction is complete.	Wassermann reaction.	Teeth, periodontal infection.	Tonsillitis.	Hematuria, grade.		
1	42 M.	12 yrs.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.51	86	7.0	170	137	6.5	12.0	12	11.0	13	—	—	0	—	+	2	
2	51 M.	1 yr.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	3.55	72	7.0	120	116	4.0	9.0	1.5	10.0	17	Complete	1	0	2	+	4	
3	21 M.	1 day	0	0	0	0	0	0	0	+	0	0	0	0	0	0	1	0	4.31	71	8.4	141	141	5.5	6.0	2.0	7.0	16	Slight	2	0	0	—	+	4
4	42 F.	3 days	Brother epistaxis	0	0	0	0	0	0	+	0	0	0	0	0	0	2	1	1.50	71	7.1	230	148	5.5	4.5	1.5	4.5	10	Marked	—	0	0	—	+	5
5	39 M.	1 yrs.	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	1	1.50	71	5.7	172	123	4.0	7.5	1.5	6.0	10	—	—	0	—	+	3	
6	49 M.	1 mon.	—	1	1	1	1	1	1	+	1	1	1	1	1	1	1	1	1.68	75	10.1	112	136	4.5	7.0	1.5	6.0	10	—	—	0	2+	+	4	
7	59 M.	20 yrs.	—	1	1	1	1	1	1	+	1	1	1	1	1	1	1	1	3.10	11	8.0	156	163	5.0	10.0	1.5	6.0	10	—	—	0	—	+	4	
8	51 F.	6 wks.	—	1	1	1	1	1	1	+	1	1	1	1	1	1	1	1	3.50	10	5.0	170	128	5.0	9.0	2.0	5.5	12	—	—	0	0	+	5	
9	51 M.	22.5 yrs.	—	1	1	1	1	1	1	+	1	1	1	1	1	1	0	0	3.62	63	5.0	124	150	4.0	17.0	3.0	11.0	10	—	—	0	0	+	0	
10	38 M.	2 mos.	0	0	0	0	0	0	0	+	0	0	0	0	0	0	1+	1	—	—	6.5	88	80	3.5	—	4.0	—	—	—	—	0	0	—	0	
11	23 M.	13 mos.	—	1	1	1	1	1	1	+	1	1	1	1	1	1	—	—	3.73	60	8.0	164	160	8.0	7.0	3.0	6.0	10	—	—	0	1	0	+	5

0, negative; +, positive; — indicates no test made.

* Black-and-blue.

0, negative; +, positive; — indicates no test made.

* Black-and-blue.

† Pyorrhea.

Probable Essential Hematuria. There were 11 cases in this group. Reference can be made to Table II for details of clinical and laboratory evidence. These cases did not differ much in important details from the group of definite cases. The average age was approximately the same. The platelet count averaged 131,000, about half the normal.

Discussion. Of the 22 cases of unquestionable essential hematuria, the platelet count was less than 150,000 per c.mm. in 12 cases (54.5 per cent); in the group of 11 cases of probable essential hematuria the average platelet count was below 150,000 in 10 cases (91 per cent). The platelet averages of 141,000 and 131,000 in the two groups are only a little in excess of one-half the normal. The decreased number of platelets, together with the positive tourniquet test, in a rather high percentage of those cases in which it was made suggests that it is possible that we are dealing with a group of cases in which bleeding occurs from a deficiency in blood platelets, as it does in cases of purpura hemorrhagica or thrombocytopenic purpura. In 2 cases in the group of unquestionable essential hematuria there was a history of easy bruising and in 1 of these a few purpuric areas had been present. In 1 case in the group of probable essential hematuria there was a history of easy bruising and there had been a few purpuric areas at times before the examination at the clinic. Symptoms and laboratory evidence of purpura hemorrhagica appeared later. No bleeding from any source has occurred since the removal of the spleen in April, 1925, when cirrhosis of the liver with moderate ascites was also found. Therefore, this case does not entirely conform to the group of true purpura hemorrhagica. Hematuria had been present for two and a quarter years before the appearance of purpura. It seems rather likely, even though the hemorrhage may be primarily due to the deficiency in platelets, that a local predisposing cause also exists. The response to local applications of silver nitrate is suggestive of a local predisposing cause, while the response to the use of the serum of the horse and of man and to injections of autogenous whole blood is suggestive of its origin in coagulation deficiency or a deficiency in blood platelets.

As normal controls, estimations of the number of platelets and of the coagulation and bleeding times, were made on 7 healthy men. An average platelet count of 198,000 per c.mm., Bogg's coagulation time of six and a half minutes and the bleeding time of two and one-tenth minutes were found. In the 12 cases of definite purpura hemorrhagica in which operation was performed at the Mayo Clinic in the last three years, 9 of which have already been reported by Giffin and Holloway,⁴ the platelet count previous to operation averaged 85,000. In cases in which there had been recent hemorrhage, not accompanied by any evidence of purpura or by essential hematuria, the average platelet count was 231,000.

The foregoing is presented in the hope that it will incite further investigation of these cases from the standpoint of the blood. There is not enough evidence at hand to prove that essential hematuria is ever localized purpura hemorrhagica or due to a deficiency of blood platelets, but the evidence is rather suggestive that this is true in some cases.

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THE RELATIONSHIP OF OBESITY TO CARBOHYDRATE METABOLISM.

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THE relation of body weight to height, age and sex and the interrelation of these with reference to the well-being of the individual has held the interest of the medical profession ever since the time of Lavoisier and many researches in this field have been made by French, German, English and American investigators. It is well recognized that a normal individual tends to maintain a certain average body weight, this average being maintained by a regular intake of water and food. In the processes of metabolism the ingested food is transformed into heat energy and is in part eliminated, the remainder being stored in the tissues in the form of combustible materials such as proteins, carbohydrates, and fats, which are readily available for the supply of energy when the food intake is not sufficient to supply the organic need. Thus, when the supply of food is in excess of the metabolic needs or when it is stored at the expense of the energy demand, this excess is stored chiefly in the form of fat and in consequence the body weight increases; on the other hand, when the supply of food is inadequate the materials previously stored are used up and there results a decrease in the body weight which, if carried far enough, produces emaciation.

In considering the significance of an increase in the body weight, three types of obesity have to be considered:

1. The *exogenous type* which is most frequently encountered, in which overweight is due to an oversupply of food. This type of

obesity may be identified by the basal metabolic rate, which in these individuals, according to Means,¹ is always within the normal limits.

2. The *endogenous type*, in which there is usually some endocrine disturbance. This group includes cases of thyroid deficiency, imbalance of gonad hormones, and of hypophyseal disturbance, each of which is characterized by a low basal metabolic rate. It is interesting in this connection to note that, as has been stated by du Bray,² the overweight in myxedema is less constant and striking than the undernutrition seen in hyperthyroidism. Following thyroidectomy, an increase in the body weight is often noted. Overweight due to an imbalance of the gonad secretions is quite commonly encountered in women after the onset of the menopause, and is also seen in animals and in man after castration. Overweight due to a hypophyseal disturbance, known as Fröhlich's syndrome, is less well understood, on account of the complex structure of the hypophysis cerebri. Investigations regarding the functions of the different portions of this gland are being carried on all over the world, and some day will aid in the interpretation of obesity due to this cause. Estimations of the basal metabolism are of great value in the study of this entire group of cases, in which, as stated above, the metabolic rate is below normal; and organotherapy, as one would suppose, is the most effective form of treatment.

3. The *constitutional type*, which has been thus tentatively designated by Strouse,³ and his coworkers. Individuals with this type of obesity are unable to lose weight even when a very low caloric diet of from 600 to 1000 calories per day is maintained for long periods of time. The basal metabolism in cases of this type is within the normal limits, and it would appear, therefore, that the metabolism of individuals in this group does not depend either on the amount or kind of food or on any endocrine disturbance, this fact making possible the differentiation of obesity of this type from the two types described above.

The relation of overweight to diabetes has been strongly emphasized in this country by Allen and Joslin. Paullin and Sauls⁴ have recently reported a series of 26 cases of obesity in relation to their carbohydrate tolerance. The ages of these patients ranged from 10 to 80; the overweight from 10 to 82.1 per cent. Unfortunately, the glycemic curves were carried for only two hours after the injection of glucose so that the interpretation of borderline cases is difficult, yet the results secured by these investigators are interesting, since in 57.6 per cent of this group the glucose tolerance was abnormal. "We feel quite strongly that the results are significant and that by a study of the glucose tolerance test, even in so small a number of patients, we have detected at least five prediabetics. Two of the five have definitely developed diabetes." It is obvious that when a clinician is confronted with an obese patient he should

TABLE I.—SUMMARY OF 12 CASES OF OBESITY.

Case number.	Age.	Sex.	Per cent. over-weight.	Glyco-suria.	Fasting blood sugar, mg. per 100 cc.	Basal metabolic rate.	Glucose tolerance.	Complaint.	Diagnosis.
1	20	F.	115	Negative	109	+	Normal	Obesity	Endogenous obesity
2	14	F.	52	Negative	112	+	Normal	Obesity; stiff neck	Endogenous obesity; fibrosis of sternocleidomastoid
3	19	F.	40	Negative	94	- 5 2	Normal	Boils; frequency of urination	Endogenous obesity
4	32	F.	32	Negative	97	+	Normal	Obesity	Endogenous obesity?
5	40	M.	80	Negative	95	+28	Normal	Slow pulse; high blood pressure	Exogenous obesity; hypertension; chronic nephritis
6	48	F.	29	+++	105		Diabetic	Pain in right hypochondrium	Diabetic obesity; chronic cholecystitis; diabetes mellitus
7	36	M.	35	+	92		Normal	Headaches	Endogenous obesity; hypertension; chronic nephritis; nondiabetic glycosuria
8	28	F.	86	Negative	95	+12	Normal	Shortness of breath	Endogenous obesity; hypertension; chronic nephritis
9	19	F.	61	Negative	107	- 8	Diabetic	Nervousness, stomach trouble	Endogenous obesity; dystrophin adiposogenitalis
10	36	F.	48	Negative	111		Predibabetic	Gas on stomach	Endogenous obesity
11	27	F.	61	Negative	111	+25	Diabetic	Amenorrhea	Endogenous obesity; diabetes mellitus
12	39	M.		+++	213		Diabetic	Dizzy spells; headaches	Endogenous obesity; diabetes mellitus

feel the responsibility of determining whether or not diabetes is present. The loss of weight which is generally considered to be a characteristic of diabetes is a phenomenon which develops later in the disease and may properly be called an "end stage." It is in connection with this problem of differentiating potential from true diabetes in obese patients that I have gathered the data regarding 12 cases of obesity in which a glucose tolerance test was made. Sufficient evidence on which to base conclusions regarding the relationship of obesity to diabetes would require the accumulated data in a series of at least 1000 cases, but this small group of cases may offer at least an indication as to the significance of obesity in its relation to carbohydrate metabolism and consequently to diabetes.

Case Reports. CASE I.—(138,940.) The patient was a woman, aged twenty years, who came to the Clinic because of obesity, her weight at the time of the first visit being 269 pounds. The personal and family history contained no significant data. There was no familial history of obesity nor was the patient a heavy eater. The patient's height was 5 feet 4 inches, so that her normal weight would have been 125 pounds. She was, therefore, 115 per cent overweight. Her blood pressure was 150 systolic, 80 diastolic.

The physical examination gave no significant information except for the obesity. A Roentgen ray examination of the skull showed that the sella turcica was normal in size. The urine showed a trace of albumin but was otherwise normal. Blood examination: White blood cells, 7000; red blood cells, 4,470,000; hemoglobin, 85 per cent. Blood chemistry: Sugar, 109 mg.; urea, 18 mg.; uric acid, 2.9 mg.; creatinin, 1.5 mg. and plasma chlorids, 605 mg., per 100 cc. of blood (all fasting values). The blood Wassermann was negative. The basal metabolic rate was +9.

The glucose tolerance curve in this case is shown in Chart I (I).

In this case the presence of some abnormal condition of the hypopituitary gland was suspected for although the roentgenogram gives no evidence of any enlargement of the pituitary body, it naturally could not demonstrate the presence of any functional changes within the gland. That such changes might well have been present is suggested by the glucose tolerance curve, which is typical of that obtained in cases of hypopituitarism, that is, it shows the carbohydrate tolerance to be above the normal.

CASE II (131,166).—This patient was a very obese girl, aged fourteen years, apparently in good general health, who sought medical consultation on account of stiffness of the right sternocleidomastoid muscle. The family history gave no significant information. She had had whooping cough, chickenpox, influenza, tonsillitis and three attacks of measles. The sternocleidomastoid muscle had begun to be stiff two years before. At the time of her first visit to the Clinic, the patient weighed 173 pounds. Her height was 5 feet 5 inches, so that her normal weight would have been 114 pounds. Thus she was 52 per cent overweight.

There was no glycosuria and the fasting blood chemistry gave the following information: Sugar, 112 mg.; urea, 24 mg.; uric acid, 2.7 mg.; creatinin, 1 mg.; nonprotein nitrogen, 27.8 mg.; plasma chlorids, 615 mg. per 100 cc. of blood. The blood Wassermann was negative.

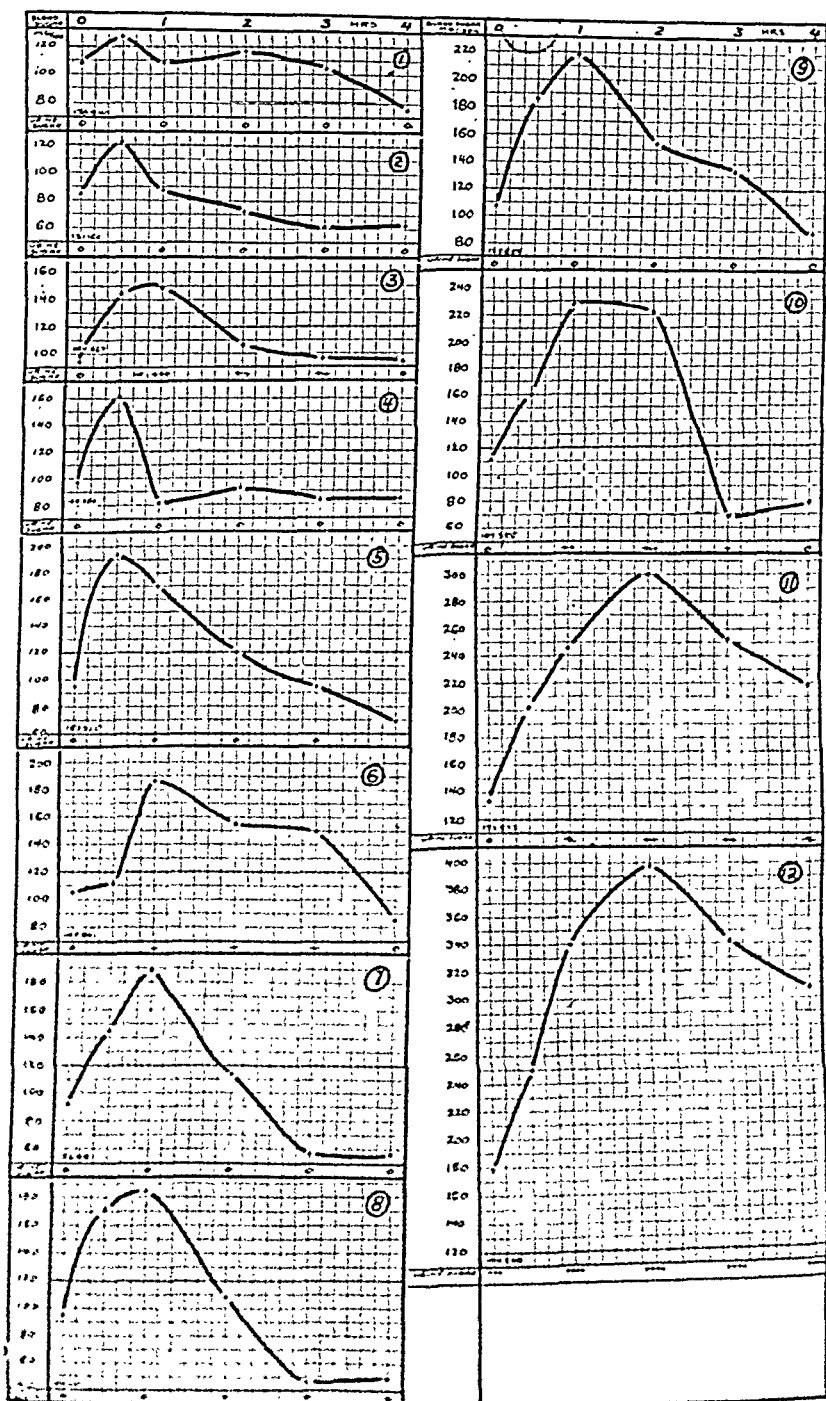


CHART I.—Glucose-tolerance curves of each of 12 cases of obesity described in text. (In each case the first reading was taken.)

A glucose tolerance test gave the normal curve shown in Chart I (II).

CASE III (104,267).—The patient, was a young woman, aged nineteen years, weighing 185.9 pounds. Her mother had diabetes, but otherwise the family history gave no significant information. The patient sought medical advice because of frequent attacks of boils during the preceding two years. She had had none of the usual diseases of childhood but had had two attacks of pneumonia during the two years before this consultation. She said that she had had occasional attacks of influenza and of tonsillitis, although a tonsillectomy and adenoidectomy had been performed six years before. Her menses were irregular, often being absent for periods of six or seven months. Her specific complaints were of boils and of frequency of urination. She had been eating very sparingly of carbohydrates, having entirely eliminated pastry and potatoes from her diet.

Physical examination disclosed a small adenoma in the right lobe of the thyroid. Otherwise no abnormalities were found excepting the excessive weight. The height of the patient was 5 feet 7 inches so that she was 40 per cent overweight. The blood pressure was 120 systolic and 60 diastolic, urine, normal. Blood examination: White blood cells 8,800; red blood cells, 4,670,000; hemoglobin, 70 per cent. Blood chemistry: Fasting blood sugar, 94 mg.; urea, 18.7 mg.; plasma chlorides 598 mg., per 100 cc. of blood. The blood Wassermann was negative. Basal metabolic rate was minus 5.2.

A glucose tolerance test gave the curve shown in Chart I (III). This is a normal tolerance curve associated with a very low renal threshold for sugar. Because of the low threshold glycosuria could easily appear during the postprandial period in such a case, and this, together with the history of boils and the obesity, would strongly suggest the presence of a diabetic condition. Yet the glucose tolerance curve shows quite clearly that the obesity in this case is not associated with diabetes, but that it is of either the exogenous or the endocrine type.

CASE IV (154,280).—This patient, a woman, aged thirty-two years, weighing 160 pounds, came to the Clinic for physical examination chiefly on account of her obesity. Her father and mother had both died of diabetes. She herself had had none of the diseases of childhood and no illnesses later in life. She was 5 feet 1 inch in height, so that she was 32 per cent above her normal weight which would have been 121 pounds. Physical examination disclosed nothing abnormal. The blood pressure was 120 systolic, 80 diastolic. Urine, normal. Blood examination: White blood cells, 9000; red blood cells, 4,560,000; hemoglobin, 80 per cent. The blood Wassermann was negative. Blood chemistry: Sugar 97 mg.; urea, 21 mg.; uric acid, 2.5 mg.; creatinin, 0.9 mg.; nonprotein nitrogen, 30.4 mg.; plasma chlorides 595 mg., per 100 cc. of blood.

The glucose tolerance curve, Chart I (IV), shows a normal tolerance for carbohydrates, thus ruling out the possibility that the overweight in this case was due to a diabetic condition.

CASE V (160,325).—This patient, a man, aged forty years, weighing 270 pounds, came to the Clinic because of a slow pulse rate and high blood pressure. The family history gave no significant information. Of the

childhood diseases, he had had measles and diphtheria and later in life he had had tonsillitis and influenza. A tonsillectomy had been performed twenty years before. He was a heavy smoker, having used from 50 to 100 cigarettes a day, although at the time of the consultation he had reduced this daily consumption to five or six. He said that a year before this consultation he had developed a pulse rate of 120 and had begun to gain weight rapidly. Eleven months before he had begun to lose weight, his pulse rate had begun to drop and his blood pressure to rise. The pulse rate had dropped to between 50 and 60 and he had been having a "feeling of tightness" about his heart. There was no dyspnea nor edema, he had a good appetite and his bowels were regular. He had no nocturia.

Physical examination revealed a well-developed but very obese man 5 feet 6.5 inches in height, weighing 270 pounds, an increase of 80 per cent above his normal weight. His blood pressure was 190 systolic, 130 diastolic; pulse rate, 72. An examination of the chest gave 100 per cent excepting that the heart showed a slight enlargement to the left; 100 per cent accentuated second aortic sound but no murmurs. Blood examination: White blood cells, 10,000; red blood cells, 5,860,000; hemoglobin, 80 per cent. The blood Wassermann was negative. A phenolsulphonephthalein kidney function test showed an excretion of 15 per cent the first and 13 per cent the second hour. The basal metabolic rate was, + 28 per cent. Blood chemistry: Sugar, 95 mg.; urea, 33 mg.; uric acid, 3.1 mg.; creatinin, 1.1 mg.; nonprotein nitrogen, 39.9 mg.; plasma chlorids, 565 mg., per 100 cc. of blood.

The glucose tolerance curve, which is shown in Chart I (V) is normal, the curve returning to the normal level in two hours. There was no glycosuria, although the blood sugar rose to 193 mg. per 100 cc. of blood, thus indicating a high renal threshold. Because of this high renal threshold it would be very difficult to detect an early onset of diabetes by urinary examination alone. The data in this case therefore show that in spite of the large increase in weight the carbohydrate tolerance is normal.

CASE VI (105,291).—This patient, a woman, aged forty-eight years, weighing 205 pounds, came to the Clinic because of pain in the right hypochondrium. Her father had died of cancer of the stomach but otherwise the family history contained no significant information. The patient had had none of the diseases of childhood; seven years before she had had an attack of gall-stone colic, which had not recurred.

Physical examination revealed a well-developed, obese woman, 5 feet 8 inches in height, whose normal weight would have been 158 pounds, so that she was 29 per cent overweight. She had a slight enlargement of the thyroid gland. Her blood pressure was 132 systolic, 80 diastolic. The physical examination gave normal findings excepting for tenderness over the gall-bladder region. A recent urine examination had shown a heavy glyco-uria but no sugar was found in the examination of the urine made at the Clinic. Blood examination: White blood cells, 7800; red blood cells, 4,860,000; hemoglobin, 80 per cent. The blood Wassermann was negative. Blood chemistry: Sugar, 105 mg.; urea, 24 mg.; plasma chlorids, 585 mg., per 100 cc. of blood.

The glucose tolerance test, the curve of which is shown in Chart I (VI), indicates the presence of a mild type of diabetes with a renal threshold between 150 and 155 mg. of blood sugar per 100 cc. of

blood. In this case of obesity, therefore, we were dealing with an early stage of diabetes.

CASE VII (132,481).—This patient, a man aged thirty-six years, weighing 250 pounds, came to the Clinic because of headaches. His mother had died of cancer of the breast, but the family history contained no other significant information. There was no history of any of the diseases of childhood nor of any other illnesses, the patient stating that he had always been in good health. A year before sugar had been found in the urine during an examination for life insurance, but he had paid no attention to this finding, even though sugar had since been found in the urine on several occasions.

Physical examination revealed a well-developed, obese man. His height was 6 feet 2 inches, so that he was 35 per cent overweight. The only abnormal finding in the physical examination was an elevated blood pressure—155 systolic, 120 diastolic. The urine showed a trace of albumin and an occasional hyaline cast. Blood examination: White blood cells, 6400; red blood cells, 4,980,000; hemoglobin, 80 per cent. Blood chemistry: Sugar, 92 mg.; urea, 45 mg.; uric acid, 3 mg.; creatinin, 1.05 mg.; non-protein nitrogen, 49.6 mg.; plasma chlorids, 595 mg., per 100 cc. of blood. The blood Wassermann was negative.

The findings in the glucose tolerance test are given in Chart I (VII), which shows that this obese man with hypertension had a normal tolerance for carbohydrates.

CASE VIII (164,227).—This patient, a woman, aged twenty-eight years, weighing 220 pounds, came to the Clinic because of shortness of breath. The family history was unimportant except that two sisters were stout. She gave no history of having had any of the diseases of childhood; but she had had frequent colds, and attacks of tonsillitis and of rheumatism. Curettage had been performed nine years before; and tonsillectomy and adenoidectomy two and a half years before. She had had a tubal pregnancy two years before; and had had five or six miscarriages. She stated that her feet swelled at times and that she had frequent suboccipital headaches. She drank a great deal of coffee. Eight years before she had weighed 105 pounds. She was 5 feet $\frac{1}{2}$ inch in height, and was, therefore, 86 per cent overweight.

The blood pressure was 144 systolic, 90 diastolic; pulse, 112. The visual fields were normal. The basal metabolic rate was +12 per cent. The urine showed a faint trace of albumin and a few pus cells. The blood Wassermann was negative. Blood chemistry: Sugar, 95 mg.; urea, 33 mg.; uric acid, 4.2 mg.; creatinin, 1.3 mg.; nonprotein nitrogen, 41.3 mg.; plasma chlorids, 615 mg., per 100 cc. of blood.

The findings in the glucose tolerance test are given in Chart I (VIII), which shows a normal tolerance curve. The marked obesity in this case is of the polyglandular type, probably principally due to ovarian dysfunction or insufficiency.

CASE IX (125,659).—This patient, a young woman, aged nineteen years, weighing 230 pounds, came to the Clinic because of nervousness and stomach trouble. The family history gave no significant information. Of the diseases of childhood she had had measles, mumps, and chickenpox; and later in life she had had attacks of tonsillitis and of rheumatism. Tonsil-

lectomy and adenoidectomy had been performed a year before. The patient stated that about every second week during the preceding year she had had a feeling of distress in the upper part of the abdomen which came on sometimes before and sometimes after eating. Eating made this distress worse and she belched gas but did not vomit. These attacks lasted from one to three days. She was very nervous and subject to frontal and occipital headaches. Her appetite varied but when it was good she ate heavily. Her gain in weight had been rapid between her tenth and eighteenth years and during the preceding five months she had gained

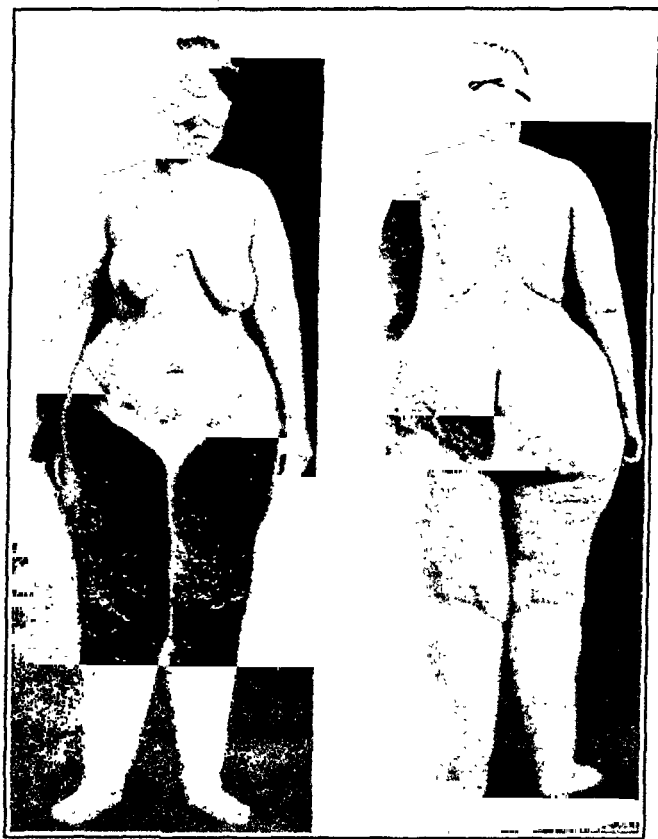


FIG. 1.—Photograph of Case IX described in text—showing the distribution of fat.

25 pounds. If she stood up for long periods she had edema of the ankles. Attacks of backache occurred after riding in an automobile. Her hands were cold but perspired most of the time. She was always tired and drowsy and exertion caused dyspnea. She had had no polyuria nor polydipsia. The menses occurred every three weeks and were very scanty in amount.

Physical examination revealed a (Fig. 1) marked adiposity of the lower part of the body. The patient was 5 feet 9 inches in height, so that she was 64 per cent overweight. She had a diffuse hyperplasia of the thyroid and a fine tremor of the hands. There was a slight murmur at the apex of the heart, which was not enlarged. The blood pressure was 128 systolic,

60 diastolic; skin, moist; hair, normally distributed over the body. A Roentgen ray examination of the skull showed no enlargement of the sella turcica. Blood examination: White blood cells, 8200; red blood cells, 4,100,000; hemoglobin, 80 per cent. Basal metabolic rate, -8 per cent. Blood chemistry: Sugar, 107 mg.; urea, 36 mg.; uric acid, 3.3 mg.; creatinin 1.3 mg.; nonprotein nitrogen, 41.4 mg.; plasma chlorids, 570 mg. per 100 cc. of blood. The blood Wassermann was negative.

The glucose tolerance test (Chart I (IX)) showed a lowered tolerance for carbohydrates, the blood-sugar curve reaching the normal level about three and a half hours after the ingestion of glucose. This curve indicates that the patient was in an early stage of diabetes. The diet, therefore, should be adjusted, especially by the reduction of carbohydrates, and the course of the patient should be followed. This case was one of adiposogenital dystrophia with a lowered carbohydrate tolerance.

CASE X (107,355).—This patient, a woman aged thirty-six years, weighing 206 pounds, came to the Clinic because of the formation of gas in the stomach after meals. The family history gave no significant information. There was no history of any of the diseases of childhood nor of later illnesses. The patient stated that she had always been well until two months before when she began to notice a progressive, painless enlargement of the abdomen. She also had a slight shortness of breath after meals. The menses were regular.

Physical examination revealed a well-developed, obese woman 5 feet 5 inches in height who was 48 per cent overweight. The blood pressure was 128 systolic, 76 diastolic. The urine was normal except for a trace of albumin. The blood Wassermann was negative. Blood chemistry: Sugar, 111 mg.; urea, 25 mg.; plasma chlorids, 545 mg., per 100 cc. of blood.

The findings in the glucose-tolerance test are shown in Chart I (X). Although the blood sugar content at the beginning of the test was normal the curve did not reach the normal level again until almost three hours after the ingestion of glucose. The height of the curve was reached during the first hour and there was a slight lagging before it began to come down, thus showing a slight lagging in the carbohydrate tolerance. This patient therefore belonged in the group of cases which we call "prediabetic" in which the diet should be regulated and the progress watched.

CASE XI (132,973).—This patient, a woman, aged twenty-seven years, weighing 205 pounds, came to the Clinic because she had not menstruated for fourteen months. The only fact of importance in the family history was that her father had died of duodenal ulcer. She had had none of the diseases of childhood, but had had tonsillitis and influenza. Her tonsils had been "clipped" nine years before. She stated that her menses had always been regular although scanty in amount. Five years before she had weighed 120 pounds. Her height at the time of this examination was 5 feet 4 inches so that she was 61 per cent overweight. She stated that she was a very small eater but nevertheless she kept on gaining weight. Recently she had been having severe headaches just above the eyes. There was no disturbance of vision. She had been drinking and voiding excessively and

perspiring freely. Exertion caused some dyspnea. She had poor endurance, slept poorly and was nervous.

Physical examination revealed an obese woman with an infantile uterus. There was no limitation of the visual fields. Roentgen ray examination showed the sella turcica to be normal. Urine examination revealed the presence of albumin and of a few casts. Blood examination: White blood cells, 13,900; red blood cells, 5,260,000; hemoglobin, 85 per cent. The blood Wassermann was negative. Blood chemistry: Sugar, 111 mg.; urea, 24 mg.; creatinin, 1.05 mg.; plasma chlorids, 555 mg., per 100 cc. of blood. The basal metabolic rate was +25 (in two estimations two months apart).

The findings in the glucose-tolerance test are shown in Chart I (XI). This is definitely a diabetic curve, showing a comparatively high renal threshold (at above 200 mg. per 100 cc.). From urine examination alone or from a fasting blood-sugar estimation, the diabetic condition could not have been identified so definitely. This case, therefore, was one of diabetic obesity, which, if allowed to go untreated, would eventually have developed into diabetic emaciation.

CASE XII (104,338).—This patient, a man, aged thirty-nine years, came to the Clinic because of dizzy spells. His father had died from apoplexy at the age of forty-nine years, otherwise the family history presented nothing of importance. He had had none of the diseases of childhood, but had had typhoid fever at the age of sixteen years, and influenza three years before this examination. The patient stated that he had been having dizzy spells and headaches which had occurred only occasionally until during the preceding month, when the dizzy spells had occurred frequently and the headache had become continuous and so severe that he had had to stop working. For the most part the headache had been unilateral and in the right occipital region but it was occasionally frontal. The patient stated that he was not able to concentrate so well as formerly, and that he was excitable and nervous.

Physical examination revealed a well-developed, somewhat obese man who did not appear sick. A slight weakness on the left side of the face was noticed when he was talking. The reflexes were hyperactive; there was impairment of the seventh cranial nerve on the left side; the tongue deviated to the left. The eye grounds were normal. The urine showed a trace of albumin and heavy glycosuria. Blood Wassermann was anticomplementary. Blood chemistry: Sugar, 213 mg.; urea, 25.4 mg.; plasma chlorids, 614 mg., per 100 cc. of blood.

The glucose-tolerance test as in Chart I (XII), gave a definitely diabetic curve.

Summary.—1. Reports of 12 cases of obesity, 3 males and 9 females, are presented, in each of which the carbohydrate metabolism was studied by means of a glucose-tolerance test.

2. The overweight in these cases ranged from 29 to 115 per cent.

3. Glycosuria was present in 2 cases in both of which diabetes was present.

4. The fasting blood sugar was normal in 11 cases, among which 4 were cases of diabetes of varying degrees of severity.

5. Among these 12 cases of obesity, 2 were definitely cases of diabetes; 3 were case of mild diabetes or "prediabetics."

Conclusion.—Although this is a small series, the high incidence of a diabetic or prediabetic condition—42 per cent—in these cases of obesity indicates the importance of investigating the glucose tolerance in all cases of obesity to determine whether or not diabetes or a tendency to diabetes may be present.

It would appear, at least, that the pancreas is to be considered among the glands, the dysfunction of any of which may be responsible for obesity of the endogenous type.

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XANTHOMA DIABETICORUM: AN UNUSUAL PROCESS OF INVOLUTION.

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THE subject of xanthoma diabeticorum was thoroughly reviewed by Major who found 74 cases reported in the literature since this disease was first described by Addison and Gull in 1850.¹ In his own article, Major² described 4 cases, and subsequently 6 additional cases have been reported. It is our purpose in this communication to describe a case showing a peculiar process of involution not mentioned in the literature. This occurred in a patient suffering from diabetes mellitus, to whom insulin was administered in the late stages of the disease.

Case Report. S. C., male, Russian Hebrew, aged thirty-one years, tailor. Family history is negative. The patient does not remember any of the diseases of his childhood and gives no history of any

serious illnesses prior to the present affliction; denies syphilis and gonorrhea by name and symptoms. He is married and has three children living and well.

About three years ago he began to have symptoms of polyuria, polydipsia and polyphagia. Urine examination revealed the presence of 5 per cent glycosuria. Under a low carbohydrate régime, these symptoms partially cleared up.

One year after the onset of the initial symptoms, he noticed small, discrete, yellowish nodules on the extensor surfaces of both legs. Six months later similar nodules appeared on both palms and elbows, and on the right thigh. The nodules gradually became confluent,

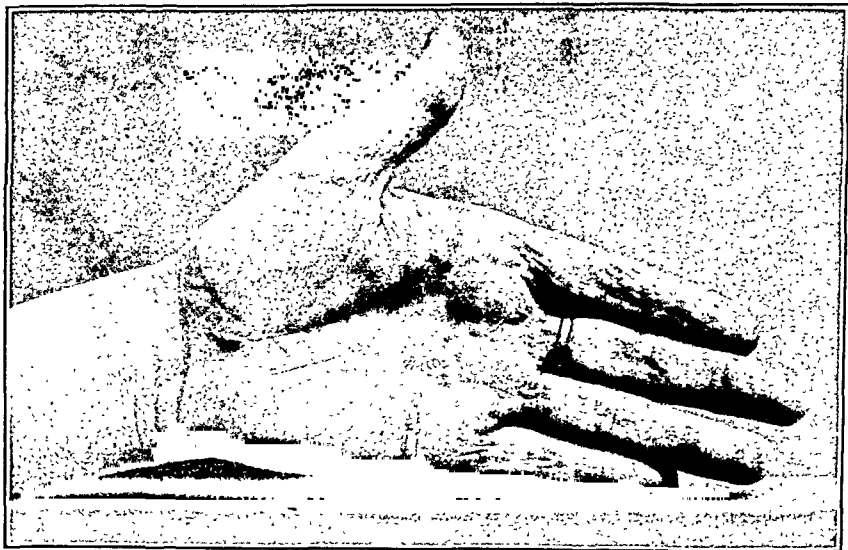


FIG. 1.—Palmar lesions.

and within several months after their onset those on the legs broke down, leaving large atrophic areas between which some of the original nodules could be readily distinguished. At no time was pruritus present. The same process occurred on the thigh, but did not involve the lesions on the upper extremities, which after attaining their maximum remained unchanged.

In the interim, he had disregarded his diet and consulted a chiropractor who gave him spinal adjustments for about one and a half years. On leaving the chiropractor's office after an adjustment May 27, 1925, the patient fell unconscious on the street, and was taken to a nearby hospital in a comatose condition, where it was found he had sustained a fracture of the base of the skull. He had marked ketonuria and a blood sugar of 430 mm. per 100 cc. of blood. Under insulin therapy he gradually recovered, and after a residence

of two weeks in the hospital was discharged with instructions to take 30 units of insulin three times a day, and to follow a low-carbohydrate diet.

At this stage the patient presented himself at our out-patient department, July 23, 1925, and stated he had no subjective symptoms. Physical examination revealed the following: well nourished, weight, 128 pounds; teeth in fair condition with some gingivitis; tonsils negative; heart and lungs normal; blood pressure, 120/80.

Skin. Both palms canary-yellow in color, presented semisolid, smooth, elevated, yellowish, peasized nodules distributed chiefly along the natural furrows (Fig. 1).* The elbows showed similar nodules of somewhat larger proportions, some of which had become confluent (Fig. 2). On the extensor surfaces of both legs and on



FIG. 2.—Elbow lesions.

the right thigh there were sharply defined areas of depressed, pigmented scars with festooned borders (Fig. 3). There was an interlacing network of these elevations upon the scars, the largest one being $5\frac{1}{2}$ inches long and $2\frac{1}{2}$ inches at its widest diameter on the left leg. In these scars the individual xanthoma nodules resembling those on the elbows, but undergoing this peculiar atrophic change, could be seen.

Histologic Examination (by Dr. David Satenstein; Biopsy Section from Leg). In the midcutis there is a more or less extensive infiltration, focal in places, but for the greater part diffuse. Smaller but similar areas are noted in the upper cutis, but not reaching to the epidermis. The infiltration is not in relation to the vessels. The epidermis is thinned but otherwise unaffected.

The infiltration is composed of more or less closely packed, long, polyhedral-shaped cells containing vesicular nuclei. In the proto-

* To Dr. Howard Fox we are indebted for the photographs and valuable suggestions in the preparation of this paper.

plasm of the cell are many very small and few larger vacuoles. The nuclei contain fine chromatin fibers and granules (xanthoma cells). In scattered places within the infiltration are rhomboidal-shaped spaces, marking the sites of former cholesterol crystals. Between and around the xanthoma cell areas are numerous fibroblasts, and occasional small bloodvessels with swollen endothelial cells. At the extreme margin of the section there is a large vessel with a proliferating endarteritis. The middle and external coats are not pathologic.

Diagnosis. Xanthoma with connective-tissue proliferation.



FIG. 3.—Lesions on the legs—note the individual xanthoma nodules.

Subsequent Course. The patient refused hospitalization, and was seen in the out-patient department for five and a half months. His diet averaged 1600 calories per day with a total carbohydrate value of 92 gm., and he administered to himself 75 units of insulin per day. It is doubtful whether he followed his diet, because during this entire period the urine was free from sugar only twice, and usually showed large amounts, at times with traces of acetone. However, in spite of the persistent glycosuria, definite improvement in the

skin lesions was observed after about six weeks' treatment. The lesions on the palms became flatter and paler, and some entirely disappeared. Those on the elbows and thigh showed similar changes but to a much lesser degree, whereas those on the legs remained unchanged.

Because of persistent glycosuria the patient was induced to enter the hospital December 5, 1925. He was placed on a diet amounting to 1200 calories and given 45 units of insulin a day. The glycosuria disappeared in two days, and the blood sugar, which had previously been estimated at 250 mg. per 100 cc., rapidly dropped to 160. He left the hospital December 21, on a diet with a caloric value of 1600, and with instructions to give himself 25 units of insulin three times a day.

During the next three months gradual improvement was apparent in his skin lesions. Those on the palms practically disappeared; those on the elbows became quite confluent and flatter and in some places completely disappeared. On the legs and thigh several of the remaining nodules could be seen undergoing the same atrophic change previously described, whereas the scars seemed to become thinner and paler, with a marked recession of the elevated festooned borders.

Within this period, he remained sugar free, although his blood sugar returned to a level of 250 mg. per 100 cc. Thereafter, however, and up to the present he has shown marked glycosuria. Blood plasma cholesterol taken just prior to his admission was 165 mg. per 100 cc., and frequent determinations never showed more than 306. Moreover, the blood plasma never had the milky gray appearance characteristic of lipemia. Repeated blood Wassermann tests were negative; the spinal fluid Wassermann test was negative (see chart).

Comment. 1. Apparently there is a definite relationship between the type of xanthoma nodule and the manner and rapidity of involution. As was emphasized by Balzer and Marie,³ the miliary type disappears much sooner than the lenticular type, because as they say "we are dealing with elements in which an incipient organization of scar tissue retards resolution." In our case the palmar lesions corresponding to the "elements miliaries" were first to improve, and two-thirds had disappeared before any improvement was noted in the "elements lenticulaires" present on the elbows, thigh and legs.

2. The question of the relationship of the glycosuria to the skin lesions has been raised by many authors. In most cases the disappearance of the glycosuria brought about either a marked improvement or a complete resolution of the lesions. The eruption, however, may disappear when the glycosuria and diabetic symptoms remain unchanged. On the other hand, diminution of sugar may find the xanthoma nodules unchanged or even worse.⁴ In our case

the skin lesions began to resolve before any reduction in the glycosuria or blood sugar was accomplished. However, the rate of improvement was notably accelerated subsequently, and although slowly, the process is still going on in spite of the return to high blood-sugar levels and marked glycosuria. Whether or not insulin has any specific effect on the xanthoma lesions, has not been determined.

CHART SUMMARIZING LABORATORY FINDINGS AND CLINICAL COURSE
WHILE UNDER OBSERVATION.

Date.	Glycosuria.	Bl. sug., mg.	Bl. chol., mg.	Diet, cal.	Insulin, units.	Remarks.
July 23, 1925	+++	1200	45	Xanthoma shows definite improve- ment.
Aug. 6, 1925	++++	200				
Aug. 18, 1925	++++	60	
Sept. 30, 1925	0					
Oct. 6, 1925	1600	..	
Oct. 14, 1925	+++					Entered hospital. Blood Wasser- mann negative. Spinal fluid Was- sermann negative.
Nov. 11, 1925	+++	250	165	75	
Nov. 27, 1925	++++					
Dec. 5, 1925	++++	200	163	
Dec. 7, 1925	0.6%	1209	45	
Dec. 8, 1925	0	
Dec. 17, 1925	0	160	306			
Dec. 19, 1925	0	125	...	1615	75	
Dec. 21, 1925	
Dec. 29, 1925	0	
Jan. 25, 1926	0	210	240	1615	75	Discharged from hospital. Marked progres- sive improve- ment in skin lesions.
Mar. 15, 1926	++++	250	185			
April 24, 1926	++++	250	306	75	

3. In view of the fact that it is generally assumed that xanthoma diabeticorum occurs as a result of a disturbed fat metabolism, the cholesterol content of the blood plasma, which may be taken as an index of the lipemia, is significant. Of the 85 cases reported (including the authors') 12 give blood cholesterol findings. The average normal blood plasma cholesterol varies between 140 and 180 mg. per 100 cc. according to the method of Myers and Wardell, although somewhat higher figures are obtained by Bloor's technique. Every one of the 12 cases shows an increase in the cholesterol content which varies from 306 to 1800 (Engman and Weiss).⁵ According to Major, and Lough and Killian⁶ a fall in the blood cholesterol leads to an improvement in the xanthoma nodules. This is not borne out in the authors' case. The first cholesterol readings in our patient were within normal limits, and his highest was 306 at a time when

the xanthoma nodules had been undergoing rapid resolution, and in face of a blood sugar of 160. It would appear that although xanthoma diabeticorum is characterized by a hypercholesterolemia, the level of blood cholesterol need bear no definite relationship to the severity of the diabetes, the blood sugar and the xanthoma lesions themselves. Similarly, the presence of hypercholesterolemia, which is occasionally part of the diabetic picture, does not necessarily imply the presence of xanthoma.

4. The consensus of opinion in the literature reviewed is that when the xanthoma nodules undergo resolution, they disappear completely or at the most leave a pigmented area over the site of the lesion. Robinson⁷ speaks of a small cicatrix at the site of the previous lesion. In his own words "after involution it mostly leaves no trace behind, but a few of the efflorescences are followed by hypertrophic cicatrices or hypertrophy of the skin."

Summary. We have here described a case of xanthoma diabeticorum in which three types of resolution went on simultaneously with little or no reference to the general condition: (a) The lesions on the palms disappeared completely; (b) those on the elbows coalesced and left large pigmented patches; (c) *those on the legs and thigh underwent degenerative changes resulting in extensive scar formation—a process hitherto undescribed.*

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DIABETIC ACIDOSIS WITH A NEGATIVE FERRIC-CHLORID REACTION IN THE URINE. REPORT OF FIVE CASES.

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CLINICIANS commonly depend upon the examination of the urine by the ferric-chlorid reaction to indicate the presence or absence of diabetic acidosis. Evidence is accumulating that a negative reac-

tion does not necessarily preclude the presence of a severe and dangerous acidosis. There have recently been observed 5 cases of diabetes with a definite clinical picture of acidosis and a low plasma carbon-dioxid content, yet with a negative ferric-chlorid reaction in the urine. We shall give a brief résumé of the literature, present 5 cases, and offer a brief discussion of the possible explanations of this phenomenon.

In the early study of acidosis in diabetes, Stadelmann,¹ von Frerichs² and Lepine,³ reported cases with apparently severe acidosis and absence of ketone bodies in the urine. In a brief communication Revillet⁵ recorded a case of diabetic coma which had a negative ferric-chlorid reaction in the urine on the day of death. Rosenbloom⁶ had 3 unusual cases of coma in which there was no trace of acetone, diacetic or β -oxybutyric acids in the urine, neither was there any evidence of kidney disease.

A fatal case of diabetic coma, whose carbon-dioxid combining power of the plasma was only 14.3 volumes per cent, while the urine contained only a trace of acetone and no diacetic acid, was reported by Feinblatt.¹⁶ There was no acetone in this patient's blood, but it was present in the spinal fluid.

The lack of a definite relationship between urinary and blood ketones, and blood carbon dioxid, in cases of diabetic acidosis has been observed by a number of workers. Fitz⁸ in several cases showed there was no definite quantitative relation between the acidosis as shown by the carbon-dioxid combining power of the plasma and the ketones of the plasma. The lack of a quantitative relationship between blood and urinary ketones was observed by Marriott.¹⁰ Finally, Allen and Wishart¹⁵ in a series of experimental studies on animals concluded that there existed no parallelism between ketonuria, ketonemia, and plasma bicarbonate content, and that death might ensue with either high or low plasma bicarbonate and with either high or low blood ketones.

The occurrence of cases of the type we are considering and records of observations such as are reported in the above paragraph, make our usual explanations of the physiology of diabetic coma and acidosis unsatisfactory in certain instances at least. Diabetic coma and acidosis is apparently not always directly due to an abnormal accumulation of ketone bodies in the blood. It was not unusual, therefore, that explanations were sought in other directions, as the following paragraphs show.

The factor of diminished blood base was early called attention to by Sellards.⁴ He reported some cases in which the excretion of ammonia and acetone bodies was normal, but which showed a decrease in the titratable alkalinity of the blood together with an increased tolerance to bases. This was taken to indicate an impoverishment in base. Campbell¹¹ demonstrated that ketones could be made to disappear from the urine under insulin therapy without a corresponding increase in the plasma carbon dioxid.

Later, Campbell and Macleod,¹² in their review on insulin, attributed this phenomenon to a deficiency in base, or perhaps some unusual combination of bases that remain in the blood and tissues. They believed, therefore, that in such conditions the use of alkali was imperative.

An unknown acid of the ketone group was suggested, as an explanation of the phenomenon we are considering, by McCaskey.⁷ He had had a fatal case of diabetic coma with neither diacetic nor β -oxybutyric acids in the urine. Bock, Field and Adair¹³ reported several cases in which, after insulin therapy, the ferric-chlorid test in the urine became negative without a corresponding rise in the carbon-dioxid content of the plasma. They found 15 cases out of 68 patients, who died from diabetic coma showing slight or no ferric-chlorid reaction in the urine. They concluded that an unknown acid other than one of the ketone group was responsible for the acidosis and recommended the use of sodium bicarbonate. Cases in which other acids than those of the acetone group seemed to be a factor in the acidosis were reported by Starr and Fitz.¹⁴ The concentration of unidentified organic acids in the urine they found to be in excess of normal, and the degree of acidosis in the blood greater than could be accounted for by the molecular concentration of the acetone bodies in the blood. They advised the administration of small doses of alkali in severe diabetic acidosis.

Impairment of kidney function, whether permanent or transient, remained to be considered. Paddock¹⁷ reported a case with very high blood sugar, having no acetone nor diacetic acid in the urine, who died three hours after admission to hospital. The kidneys at autopsy showed a mild degree of subacute nephritis. The urine had a specific gravity of 1.020, a trace of albumin and a few hyaline casts. Argy's¹⁸ case had the unusual blood sugar of 1714 mg. per 100 cc. with no acetone nor diacetic acid in the urine. There were many hyaline casts and a cloud of albumin. The non-protein nitrogen of the blood was 154 mg. Autopsy showed among other things, chronic parenchymatous nephritis, focal liver necrosis with fatty degeneration, and interstitial fibrosis of the pancreas. An interesting case was reported by John¹⁹ in which the carbon dioxid in the plasma remained at a persistently low level in spite of large doses of insulin. A marked urinary retention developed, however. The blood urea was very high and the phenolsulphone-phthalein output was greatly reduced. With improved kidney function the carbon-dioxid volume of the plasma increased. Edema of the tissues developed a few days after the inception of treatment. John suggested that perhaps the low carbon-dioxid values were due to kidney retention and edema of the tissues. Lemann²¹ has recently reported a case which was in coma several times without showing acetone or diacetic acid in the urine. A nephritis, however, was found to coexist.

Peters²⁰ published an exhaustive study of the blood chemistry in diabetics. He stated that "severe ketonemia with minimal ketonuria as a terminal event in diabetes has been encountered not infrequently." Cases of severe diabetes, he found had a reduction in the total base and also in the plasma chlorids. When ketosis is of slow development it may reach a considerable degree of severity without affecting the plasma bicarbonate. In such cases the plasma chlorid is reduced and it is supposed that the base thus freed combines with the excess of organic acids for their neutralization. In more severe cases and those developing more rapidly, base is derived from both sodium chlorid and sodium bicarbonate, and hence both are lowered. As regards therapeutics, he believes that intravenous saline injections are logical. If the acidosis is due to an over-accumulation of ketone bodies, the proper adequate use of insulin and carbohydrate will eliminate them and the administration of sodium bicarbonate will tend to produce an alkalosis, especially as a considerable amount of base will be released by the combustion of the ketone bodies. He remarks that the acidosis in diabetic coma may be caused in part by acids not of the acetone group, but by acids formed as a result of associated pathologic processes. Case XXXVI, for example, in this series was in diabetic coma but had marked ketonuria and yet the serum contained only 13.5 millimols of organic acid, which is within the limits of normal.

Methods: The methods we have used in making the determinations reported here are given in Appendix I, at the end of the paper.

Case Abstracts. CASE I.—W. S., a white boy, aged seventeen years, was admitted (November 14, 1925) in a comatose condition and it was his third entry to the hospital in such a condition. He was a known diabetic for four years. His first admission, May 14, 1923, was ushered in by an attack of acute abdominal pain and vomiting. He had a high blood sugar, a low-plasma carbon dioxid and his urine contained sugar, acetone and diacetic acid. He improved on insulin and was discharged after four months with a blood sugar of 187 mg.

The second entry was on January 31, 1924. He showed a tendency to superficial abscess formation at the site of the insulin injections and had many scars from the abscesses. A culture from these lesions showed *Streptococcus hemolyticus*. He was discharged March 12, on the following diet: Protein, 50; fat, 105; carbohydrate, 50; insulin 30-10-15, units per twenty-four hours. The blood sugar was 142 mg. The urine showed a trace of albumin, sugar and acetone; but no diacetic acid. He was then under the supervision of the medical dispensary. Frequent colds, boils and some abscessed teeth, however, were his lot. The day before admission he developed labored breathing and became stuporous that night.

Past Medical History and Family History. Irrelevant.

Physical Examination. The temperature, pulse and respiration were 96°; 108; 34. Patient was semicomatose but could respond by answering "yes" and "no" to questions. He cooperated slightly on examination and could swallow. His lips were pink, his respirations deep and his breath had a fruity odor. The intraocular tension was decreased. There was considerable pyorrhea. Numerous scars of old infections presented on his thighs, and the left thigh was the seat of a large, red, fluctuating area.

TABLE I.

Case 1.—W. S.—Age, seventeen years; height, 170 cm.; weight, 114 pounds; basal requirements, 1650 calories.

Date.	Diet.				Insulin, units.		Urine.				Blood.			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.			Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO ₂ plasma.	Ketones.	
Nov. 20	4	0	789	3972	..	420*	..	+	+	+	+	+	+	White blood cells, 22/100; hemoglobin, 87 per cent; blood pressure, 116/65; semicomatose; temperature, 96°; pulse, 108; respiration, 34.
Nov. 21	11	0	336	1388	..	117*	3.50 P.M.	+	+	+	+	11	..	Blood culture, negative.
							11.30 P.M.	+	+	+	+	13	..	
							9.00 A.M.	+	+	+	+	33	..	
22	50	39	121	1035	20	20	1.15 P.M.	+	+	0	..	33	..	Titrable acidity of 24-hr. urine, 325 cc., N/10 NaOH; blood urea nitrogen, 17 mg. 2 hrs.; 20 per cent in 5 hrs.; total, 45 per cent in 5 hrs. Blood urea nitrogen, 23.
							8.30 P.M.	+	+	0	385	
							8.40 A.M.	+	+	0	
23	58	41	116	1005	20	20	9.00 P.M.	+	+	0	..	46	..	
							9.00 A.M.	+	+	0	385	51	..	
							...	136	+	+	327	
Dec. 24	57	41	121	1081	20	20	...	0	+	0	
Dec. 24	57	104	53	1377	35	0	...	0	+	0	

* Total.

The heart was negative, but there were scattered rales throughout both chests. The abdomen was negative and knee jerks were not obtained. The urine on admission showed sugar + + + +, and diacetic acid + + +. The blood sugar was 319 mg. and the CO₂ content of the plasma was 11 volumes per cent. Table I is an abridged record of his stay in the hospital.

Clinical Notes. The carbohydrate given at first was in the form of orange juice reinforced with sucrose. This was given by mouth. Enteroclysis of 3 per cent sodium bicarbonate and 5 per cent glucose was also given. There were no intravenous injections and no alkali was given by mouth. Large doses of insulin were given hypodermically, 420 units in the first twenty-four hours and 117 the next. Frequent urine analyses were made to prevent overdosing and hypoglycemia.

The interesting feature of this case is the fact that for thirty-six hours at least, the urine was free from diacetic acid according to the ferric chlorid test, and yet, the carbon-dioxid content of the plasma was only 33 volumes per cent. The discrepancy between the absent ferric-chlorid reaction in the urine and the low carbon-dioxid content of the plasma need explanation. There was some evidence of impaired renal function, for the urine contained a cloud of albumin, few epithelial, and many light granular casts.

On the third day the phenolsulphonaphthalein test showed delayed elimination. The fourth day the blood urea nitrogen was slightly increased. We had no further test of the blood urea or phenolsulphonaphthalein elimination, but the urine itself cleared up, except for a very faint trace of albumin. The impression was held, therefore, that the kidney was suffering only a temporary or functional disability. Even at that time, however, its output of total acids was in the normal range.

CASE II.—M. Q., a white female, was admitted (January 8, 1926) in coma; but her physical condition was such that she was sent to the surgical wards with the possibility of an acute abdomen. Her abdomen was apparently rigid and her leukocytes 30,000. This rigidity, however, was later decided to be only inspiratory and not due to visceral disease.

History of Present Illness. Patient was a known diabetic with characteristic symptoms of three years' duration. She was well controlled by diet and insulin until December, 1924, when, after discontinuing insulin for one week, she went into coma. This cleared up in four days with insulin and she did well until December, 1925, when she began to disregard her diet. Four days before admission she developed epigastric pain and sweating. She grew progressively weaker, felt drowsy and finally went into the condition described on admission. There was no history of an acute infection.

Previous Medical History. Quinsy at twelve years of age.

Family History and Social History. Irrelevant.

Physical Examination. Temperature, pulse and respiration 96°; 104; 17. The breath had a strong odor of acetone. The respirations were deep and grunting. The skin was dry and loose. The patient could scarcely be aroused enough to say "yes" or "no."

The blood pressure was 100 to 80 and the radial pulses were of poor volume and tension. There was a short, blowing, systolic murmur over the base of the heart—not transmitted. The knee jerks could not be elicited. The examination was otherwise negative. The urine showed sugar, + + +; acetone, + + +; diacetic acid, + + +. The blood sugar was 482 mg. per 100 cc. and the plasma CO₂ had the low figure of 6.8 volumes per cent. Table II gives a summary of the essential features of the case.

Clinical Notes. The simulation of a surgical condition on entry was an interesting feature of this case. The apparent rigidity and leukocytosis were misleading factors. It was later decided that the rigidity was only

TABLE II.

Patient, M.Q.—Age, forty-seven years; height, 5 feet; weight, 102 pounds; basal requirements, 1200 calories.

Date.	Diet.				Insulin, units.	Urine.				Blood.			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.		Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO ₂ plasma.	Ketones.	
Jan. 9	5.30 P.M.	++	++	++	452	6.8	..	Comatose; blood pressure 100/80; temperature, 96°; pulse, 120; respiration, 24.
	0	0	265.	1060	Tr.	+	0	77	27	..	Hemoglobin, 120 per cent; red blood cells 5,900,000; white blood cells, 24,000; blood urea nitrogen, 43 mg.; urine, albumin, cloudy, no casts.
						11.00 A.M.	Tr.	Tr.?	0	40.4	Phenolsulphonethalein: 1st hr., trace, 2d hr., 28 per cent; 4th hr., 20 per cent; total in 4 hrs., 40 per cent. See special chart. Table IIa.
10	25	30	120	850	..	10.00 P.M.	++	Tr.?	0	Urine, trace of albumin; occluded hyaline casts.
						...	++	Tr.?	0	470	20	..	White blood cells, 17,300; hemoglobin, 105 per cent; 12-hr. urine, 760 cc.; total acidity, 180 cc., N/10 NaOH.
						10.30 A.M.	++	Tr.?	0	Blood pressure, 140/90; stuporous.
11	46	34	289	1566	..	6.00 P.M.	++	+	+	Urine, albumin, cloudy, hyaline casts.
						10.00 P.M.	++	+	Tr.	
						24-hr. sp.	4.9	+	0	44	48	..	
12	30	27	255	1419	..	4.00 P.M.	0	0	0	
13	50	46	85	954	36.7	0	0	89	48	..	
19	51	100	76	1408	20	...	7.5	0	0	201	61	..	Blood urea nitrogen, 17 mg.; phenolsulphonethalein: 1st hr., 55 per cent; 2d hr., 5 per cent; total in 2 hrs., 60 per cent.
					5	...	+	0	0	261	

* Total.

inspiratory and the urine analysis pointed the way to the diabetic condition. Other cases of ours have shown a leukocytosis, the degree of which probably cannot be accounted for by dehydration if we use the hemoglobin percentage as an indication of the degree of dehydration. Neither can the leukocytosis be accounted for here on an infectious basis for we were unable to find a focus of infection; and Roentgen rays of teeth, sinuses and gall bladder, were negative. There is, perhaps, some factor associated with the metabolism of diabetic coma which chemically stimulates leukocytes. Peters²⁰ in his article reported that several of his patients narrowly escaped the surgeon's knife because of a simulated acute abdominal condition.

During the first twelve hours in the hospital it became difficult for the patient to swallow. Through a nasal tube, feedings of orange juice were then given. But rather intractable vomiting developed and we were considering intravenous injections, when we tried milk sweetened with sugar and found that this was well tolerated.

It seemed almost as if the patient had a specific sensitivity to orange juice for immediately after vomiting orange juice, milk was kept down. Grape juice, prunes, bananas, toast and sweetened milk were tolerated when orange juice and oat-meal actually induced vomiting. The patient ultimately came out of her coma completely, although we did not expect it, and she left the hospital before her diet had been adequately adjusted.

Twelve hours after admission there was an absent ferric-chlorid reaction in the urine together with a CO₂ content of the plasma of from 20 to 27 volumes per cent. These combined findings persisted for over twenty-four hours. If we had judged alone from the ferric-chlorid test and the improved mental state of the patient, we certainly should not have imagined that the carbon-dioxid content of the plasma was so low as 20 volumes per cent. It is obvious that these rather simple laboratory and clinical tests are not always, at least, indicative of the degree of "acidosis" that actually exists.

Impaired renal function occurred in this case as was indicated by: (1) A cloud of albumin and casts in the urine; (2) a blood-urea nitrogen of 43 mg.; (3) a phenolsulphonaphthalein test which showed only a trace the first hour, 28 per cent the second, and 20 the fourth, making a total of 48 per cent in four hours.

As in the previous case, however, the renal function was only temporarily impaired, for later the blood urea nitrogen fell to 17 mg.; the phthalein test was 60 per cent in two hours; and the urine showed only a very faint trace of albumin. The decreased kidney function could not have been due to circulatory collapse for the blood pressure the day after admission was 105 to 80, approximately the same as on entry. One might suppose that a sort of functional or transient nephritis existed on a dehydration basis, for the hemoglobin of 120 per cent certainly was evidence of this.

Table IIa shows determinations* of the plasma electrolytes for the patient, and also figures for the normal person. The blood ketones were increased

TABLE IIa
Plasma Electrolytes.

Patient.		Normal.	
Cations (m. equiv.).	Anions (m. equiv.).	Cations (m. equiv.).	Anions (m. equiv.).
Total, 126	HCO ₃ . . . 11.5	Total, 150	HCO ₃ . . . 26
	Cl . . . 97.3		Cl . . . 103
	PO ₄ . . . 0.5		PO ₄ . . . 3
	Ketones . . . 4.9		SO ₄ . . . 1
	Proteins† . . 12.0		Prot. . . 17

* Our thanks are due Dr. Austin, of the Department of Research Medicine, for these and other analyses, and his kind cooperation.

† Difference.

but not enough to account for the decrease in the CO_2 . The latter is accounted for by another determination, viz., the total base of the plasma. In our patient, the measurement of total base equalled 126 milliequivalents. Lowered total base then in part accounts for the total CO_2 content of the plasma. Peters²⁰ made numerous determinations in diabetics and found the same condition of plasma electrolytes. Our case is merely a single confirmation of his observations. It shows the mistaken reasoning that can follow the finding of an absent ferric-chlorid reaction in the urine, and that the plasma CO_2 content may leave one with wrong conclusions according to one's usual reasoning about low CO_2 and acidosis.

CASE III.—L. C., a white female, aged forty-two years, was admitted January 7, 1926.

Chief Complaint. Weakness. Sense of oppression in chest. Indigestion. Tapeworms.

History of Present Illness. The patient had lost considerable weight in the past several years. Six months before entry she had noticed paresthesia of the fingers and toes. She passed large quantities of urine and had nocturia two to three times. One week before admission the patient had a sudden attack of indigestion which was characterized by vomiting and gaseous eructations. Associated with this there was a sense of oppression in her chest. She was confined to bed and grew progressively weaker until the time of admission.

Past Medical History. Tapeworm infestation seven years ago and has continued to pass segments occasionally since. Breast abscess seven years ago.

Family History. Irrelevant.

Physical Examination. Temperature, pulse, respiration, 97°; 104; 20. Blood pressure 138/82. Patient was a poorly developed, emaciated and dehydrated woman. She was sluggish mentally. Her tongue and pharynx were exceedingly dry and red. Over the apex of the heart there was a faint systolic bruit. The knee and ankle jerks were not elicited. Examination was otherwise negative. The urine on admission showed negative albumin; sugar, ++; acetone, +++; and diacetic acid, ++. The leukocytes were 16,000 and the hemoglobin, 100 per cent. The accompanying table gives the important points in this case.

Clinical Notes. Attention is called in this case to the following: 1. The occurrence of a low plasma CO_2 content (22 to 37 volumes per cent) for a period of over twenty-four hours, with a negative ferric-chlorid reaction in the urine, on repeated examinations.

2. With a negative ferric-chlorid reaction in the urine, the blood ketones were 50.7 mg. per 100 cc., a figure well above normal. This suggested the possibility of a high renal threshold for ketones.

3. There was also a retention of urea nitrogen (57 mg. per 100 cc.) and a delayed phthalein elimination (first hour, 7 per cent; second hour, 50 per cent) together with albumin and casts in the urine. These evidences of nephritis cleared up later with the disappearance of the dehydration, as was shown by a blood urea nitrogen of 12 mg. per 100 cc., a phthalein test of 50 per cent the first hour and 5 per cent the second, and a urine negative for albumin and casts.

4. The importance of the hemoglobin percentage as an indication of dehydration (100 per cent on admission and 70 per cent on the fifth day).

5. It is of interest to note that in spite of a plasma carbon dioxide of 22 volumes per cent there was no noticeable hyperpnea.

6. A possible factor which perhaps precipitated the acidosis in this case was an old intestinal infestation with *Teneo Saginata*, for segments were found in the feces during the patient's residence in the hospital.

TABLE III.

Patient, L. C.—Age, forty-two years; height, 5 feet, 2 inches; weight, 90½ pounds; Basal requirements, 1220 calories.

Date.	Diet.				Insulin, units.	Urine.				Blood			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.		Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO ₂ plasma.	Ketones.	
Jan. 8	190	760	..	90*	...	++	++	++	316	..	Hemoglobin, 100 per cent; white blood cells, 16,000.
9	58	34	120	818	..	60*	1.00 P.M. ++ 55	+	0	211	37	51+	Blood urea nitrogen, 57 mg.; phenolsulphonophthalein: 1st hr., 7 per cent; 2d hr., 50 per cent; total 2 hrs., 57 per cent. Hemoglobin, 70 per cent; white blood cells, 8400.
13	56	104	52	1368	20	15	...	6.4	0	242	64	..	Blood urea nitrogen, 12 mg.; phenolsulphonophthalein: 1st hr., 48 per cent; 2d hr., 5 per cent; total 2 hrs., 53 per cent.
16	
Feb. 28	50	140	70	1740	15	0	10	0	0	0	

* Total.

CASE IV.—E. G., a white female, aged fifty-seven years, was admitted January 20, 1926.

Chief Complaint. Dimness of vision. Generalized weakness.

History of Present Illness. The onset of the patient's diabetic symptoms occurred eleven years before entrance to the hospital, with itching of the skin, excessive thirst, polyuria, nocturia, and a craving for sweets. Five years before admission the patient had an ulcer on her foot and came to this hospital for treatment. At that time her blood sugar was found to be 300 mg. per 100 cc.; her blood urea nitrogen 33 mg., and her blood pressure was 128/70. Her urine showed a trace of sugar, a cloud of albumin, and a few hyaline and light granular casts. The phenolsulphonephthalein test was 35 per cent on admission and 65 per cent on discharge.

Physical examination was essentially negative. After six weeks she was discharged sugar free, with a blood sugar of 172 mg. and a blood urea nitrogen of 26 mg. per 100 cc. The diagnosis on discharge was chronic nephritis and diabetes mellitus. Since leaving the hospital she had been under her physician's care and remained sugar free. However, during the past four months she noticed increasing dimness of vision and an occasional headache. Her bowels were constipated.

Past Medical History. Irrelevant.

Physical Examination. Temperature, pulse, respiration, 98°; 96; 26.

The patient was a well-developed, somewhat fat, woman, aged fifty-seven years. Her vision was markedly impaired. Her pupils were equal, slightly irregular, and reacted poorly to light.

The fundi showed numerous hemorrhages, exudates and areas of atrophy. The brachial vessels were tortuous and thickened. Her blood pressure was 215 to 115. The heart was slightly enlarged, with sharp sounds of embryonic quality. There was a precordial, systolic murmur. The lungs were negative and the abdomen pendulant. The extremities were negative and the arteries were felt pulsating at both ankles. Urine showed: A trace of sugar with acetone and diacetic acid negative; a cloud of albumin; no casts; no red cells and two pus cells per high-power field. The hemoglobin was 74 per cent and the leukocytes 7600. Table IV is an abridged record of this case.

Clinical Notes. The combination of diabetes and nephritis in this patient makes some of our determinations more interesting. On entry there was no clinical evidence of acidosis. We were surprised on the following morning to find the CO₂ content of the plasma 38 volumes per cent. With a phenolsulphonephthalein excretion of only a trace in two hours and a blood-urea nitrogen of 56 mg., we concluded that the condition was chiefly nephritic. We placed the patient on a low-protein, low-salt, diet with rather high carbohydrates and fat. She had shown only a trace of sugar, no diacetic acid nor acetone, and her blood sugar was only 164 mg. per 100 cc. On this régime we gave her 15 units of insulin in the morning.

Six days after admission, with the treatment as above outlined, we found the blood and urine analyses approximately the same as on entry, but the patient felt better subjectively. Her blood pressure was lower, her headaches were not so severe and her vision was slightly but definitely better. The following day, however, the CO₂ content was 29 and 27 volumes per cent, respectively, on two determinations three hours apart. The urine contained sugar, +; no diacetic acid; no acetone. There was, however, a heavy cloud of albumin but no casts. It was felt on this day that the patient's general condition was improving, until we received the report of the low CO₂ content of the plasma.

The following day the ketones of the blood were determined and to our astonishment they were 153 mg. per 100 cc., with no acetone nor diacetic

TABLE IV.

Patient, E. G.—Age, fifty-seven years; height, 5 feet, 5 inches; weight, 145 pounds; basal requirements, 1440 cal

Date.	Diet.				Insulin, units.	Urine.				Blood.			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.		Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO ₂ plasma.	Ketones.	
Jan. 23	51	153	79	1897	Tr.	0	0	164	38	..	Homoglobin, 74 per cent; phenolsulphon- epithalain, trace in 2 hrs.; blood urea nitrogen, 56 mg.
25	36	119	130	1734	15	..	+	0	0	164	Blood urea nitrogen, 42 mg.; blood uric acid, 4.8 mg.
29	36	122	132	1770	15	..	+	0	0	180	42	..	Blood urea nitrogen, 50 mg.; urine: sp. gr., 1010; albumin, cloud; casts, few, waxy, epithelial and granular.
30	38	142	106	1842	15	2.00 P.M. 5.45 P.M.	+	0	0	..	29 27	..	See Chart.† IVa.
Feb. 2	34	124	122	1740	15	..	0	0	0	173	24	153	Blood urea nitrogen, 49 mg.; blood pres- sure, 180/94.
9	28	121	58	1426	15	..	0	0	0	252	Blood urea nitrogen, 100 mg.
12	70	280	0	..	Incontinent	182	27	..	Blood urea nitrogen, 152 mg.; comatose.
13	9	1	180	804	0	0	0	16	Urine: albumin, cloud no casts. Death, 8.35 P.M.; autopsy not permitted.

* Total.

acid in the urine. The CO_2 content was 24 volumes per cent and the blood urea nitrogen 49 mg. Obviously we had unwittingly allowed the ketones to develop in the blood, but neither the clinical condition of the patient (no dyspnea nor increased drowsiness) nor the urine analysis gave us a clue to the real state of the metabolism. The threshold for ketone body elimination was obviously raised by the actual nephritis. The day following these determinations, the patient developed hyperpnea and the blood urea rose to 100 mg. per 100 cc. of blood. Increased doses of insulin were given to reduce the ketohemia but the patient steadily failed, went into coma and died three days later. Her blood ketones had been removed, however, by the increased insulin, for on the day of death the blood ketones were only 16 mg. per 100 cc. The blood urea, however, mounted to 152 mg., the day before exitus.

Table IVa records some observations made on January 30, 1926, when there was no acetone nor diacetic acid in the urine according to the ferric-

TABLE IVa.

Plasma electrolytes.

Patient.			Normal.		
Conductivity of plasma.	Plasma protein by refractometer.	Depression of freezing point.	Conductivity of plasma.	Plasma protein by refractometer.	Depression of freezing point.
0.822	9.7%	59	0.785-0.810	7%	54-57

chlorid test, with a CO_2 content of the plasma of 29 to 27 volumes per cent. Normal figures are given for comparison. The conductivity of the patient's plasma was increased and this is taken as an indication of increased base in the plasma. The determination of the CO_2 content of the plasma leaves us ignorant as to the amount of total base in the plasma, whether it has decreased, in carrying out ketones and end products in the urine, or whether merely the base is combined and not available for other acids. The determination of the plasma conductivity in this case shows us that (although the CO_2 content is low) the total base is somewhat above normal and that it is, therefore, probably combined with acid products of metabolism, although the urine has not given us indication of this.

CASE V.—M. R., a white female, aged sixty-four years, was admitted February 2, 1926.

Chief Complaint. Coma.

History of Present Illness. The patient was a retired physician who came into the Hospital in a semicomatose condition. The history was unsatisfactorily obtained. She had apparently had glycosuria, however, for almost a year, but had apparently controlled her diabetes by diet alone, for she never had taken insulin. The day of entry she became drowsy and developed deep, sighing respirations. A local physician visited her and sent her to the hospital.

Previous Medical and Family History. One breast was removed for cancer several years before entry. A brother had severe diabetes.

Physical Examination. Temperature, pulse, respiration, 96°; 116; 40.

The patient was in a semicomatose condition but responded intelligently, although slowly, when pressed for answers. She cooperated on examination, and with the nursing, and was able to swallow. She was hyperpneic, had pink lips, and acetone on her breath. She was thin and somewhat dehydrated. Her blood pressure was 65/40. The heart was negative and there was nothing unusual in the chest. The abdomen was also negative

TABLE V.

Patient, R.—Age, sixty-four years.

Date.	Diet.				Insulin, units.	Urine.				Blood.			Remarks.
	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.		Time of test.	Glucose.	Acetone.	Diacetic acid.	Sugar.	CO ₂ plasma.	Ketones.	
Feb. 2	:	:	:	:	:	...	+	+	0	450	14.7	194	Comatose; blood pressure, 65/40; blood urea nitrogen, 47 mg.; plasma proteins, 77 per cent; hemoglobin, 80 per cent; white blood cells, 24,900. See Table Va. Urine: albumin, very faint trace; casts, many hyaline and few granular.
	:	:	:	:	250*	11.00 P.M.	+	+	0	468	39	..	
3	:	:	:	:	:	9.00 A.M.	+	0	0	353	
	:	:	:	:	:	3.00 P.M.	Tr.	..	0	150	
3	:	:	:	360	100*	7.30 P.M.	

* Total.

and the knee jerks were normal. There was no evidence of infection. Urine examination showed: Specific gravity 1.020; a cloud of albumin; positive sugar; acetone, ++; diacetic acid negative; a few waxy and hyaline casts; no red blood cells and three white blood cells per high-power field. The blood sugar was 450 mg. per 100 cc. and the CO_2 content of the plasma was 14.7 volumes per cent. The blood urea nitrogen was 47 mg. and the plasma proteins were 7+ per cent determined by the refractometric method. Her hemoglobin percentage was 80 and the leukocytes were 24,900. About twenty-six hours after entry she became unconscious and died three hours later. Table V is an abstract of her record.

Clinical Notes. The patient's record shows that she never had a positive ferric-chlorid reaction in the urine, yet she unquestionably died of diabetic coma. She was considered a mild diabetic and the day she became drowsy it was not believed that a condition was developing which called for rapid action. An analysis of her urine by the ferric-chlorid method would not warn us that acid poisoning was threatening. The low CO_2 content of the plasma showed us that an advanced acidosis existed but this test of course, is not available in the home.

We note in her chart a high value of blood ketones (194 mg. per 100 cc.) with an absent ferric-chlorid reaction in the urine. Some of the urine analyses were made on catheterized urine. Two hours before death a catheterized specimen showed only a trace of sugar and no diacetic acid.

Table Va shows some further determinations made on the blood taken on entry which showed a low CO_2 content, and a high sugar and ketone content. The conductivity which is lower than normal, indicates a lowered plasma base. The protein content indicates dehydration.

TABLE Va.

Plasma electrolytes.

Patient.		Normal.	
Conductivity of of plasma.	Plasma protein by refractometer.	Conductivity of plasma.	Plasma protein by refractometer.
0.704	8.4%	0.810-0.785	7%

An autopsy was performed which showed a rather friable liver in the gross with nothing characteristic microscopically, a pancreas exceedingly infiltrated with fat, a heart with brown atrophy and kidneys with no gross or microscopic evidence of nephritis. The threshold for ketones here, therefore, was not raised by a *true nephritis* but probably was due to a *transient or functional nephritis* again on a dehydration basis.

Discussion. In the present report we have presented the records of 5 patients suffering with diabetes mellitus, who at some time in the course of this disease presented the unusual combination of a low CO_2 content of the plasma with a negative ferric-chlorid reaction in the urine. The possible explanations of this condition are:

1. A transient, functional nephritis, or better, temporarily impaired renal function on a basis of dehydration causing a high threshold for both blood ketones, nitrogenous and other acid products of metabolism.

2. Actual nephritis with diabetes, causing a retention of the same products as in 1.
3. Lowered base in the plasma.
4. Unknown acid in the blood.
5. A combination of the above explanations.
6. An unusually rapid decomposition of diacetic acid into acetone in the urine.

We believe the following explanations account for our various cases:

Case I. Possibly mechanisms 1, 3, 4. We had definite evidence of impaired renal function in the urine (which later cleared up) and in the phenolsulphonephthalein test.

Case II. Mechanisms 1, 3. There is no doubt that temporary renal impairment existed here for we had a pathologic urine (a cloud of albumin and casts), a pathologic blood (urea nitrogen 43 mg.) and a pathologic phenolsulphonephthalein test (trace in the first hour, 28 per cent in the second). After clinical improvement all of these values returned to normal. The renal impairment was not caused by circulatory failure, neither was it caused by infection, because both of these factors were wanting. The most probable explanation seems to us to have been dehydration and the hemoglobin percentage of 120 was ample evidence of this. We might picture therefore, a sort of functional nephritis existing on the basis of dehydration and that the threshold for ketone body and other acid products of excretion was elevated. Such a dehydration acidosis is known to exist in diseases of infancy and childhood.⁹

The question comes up then as to whether the transient nephritis could have accounted for the acidosis. Actual determinations, however, showed an increase in the acid products of the blood, but not sufficient to account for the low CO_2 content of the plasma. The figures in Table II show an increase in blood ketones above normal. Normal blood contains less than 4 mg. of hydroxybutyric acid and 1.5 mg. of acetone and diacetic acid per 100 cc.^{22,29} In the patient's blood we found 40.4 mg. of ketone bodies—a figure definitely above normal, but the increase in ketones is not great enough to account for the decrease in CO_2 . The latter is accounted for by the lowered total base in the plasma. In our patient the measurement of total base equalled 126 milliequivalents, whereas normal blood contains 150 milliequivalents.

We have in this case, substantial evidence of a temporary impairment of renal function which no doubt raised the threshold for blood ketones which were increased, and which, therefore, in part accounts, no doubt, for the absent ferric-chlorid reaction in the urine. The mechanisms of the lowering of the CO_2 in the plasma we have accounted for in the preceding paragraph and it is a mechanism of physiology which one usually does not think of when he obtains a low plasma CO_2 in diabetic acidosis. With such findings, we

believe, it is rational to consider intravenous sodium chlorid or possibly sodium-bicarbonate injections.

Case III. Mechanism 1, possibly 3.

Case IV. Mechanisms 1, 2. This case presented the combination of severe, fatal chronic nephritis with a moderate diabetes. It, therefore, furnished almost a laboratory experiment of the effect of renal-function impairment on the threshold for ketone-body excretion. With the blood ketones at a level of 153 mg. per 100 cc., no acetone or diacetic acid, was found in the urine by the usual tests! There was, too, some dehydration as the refractometric examination of the blood showed.

If we convert the ketone (153 mg. per 100 cc.) and CO_2 (24 volumes per cent) values into milliequivalents, we have 26.4 and 10.7 milliequivalents, respectively. The lowering in the CO_2 did not release, therefore, sufficient base to combine with this amount of ketone bodies. The assumption may be made therefore, that the chlorids were reduced and yielded increased base, and that the shifting of the pH toward the acid side released more base from the plasma proteins. As a matter of fact the electrical conductivity measurement showed an increase over normal, which is an indication of increased base in the plasma. The determination, alone, of the CO_2 content of the plasma leaves us ignorant as to whether the total base of the plasma has decreased (in carrying out ketones and end products in the urine) as for example in Case II; or whether merely the base is combined and not available for other acids.

Case V. Mechanisms 1, 3.

Autopsy in this case proved that there was no actual nephritis; yet this patient went into diabetic coma and died without showing a positive ferric-chlorid reaction in the urine. With blood ketones at 194 mg. per 100 cc. the ferric-chlorid reaction in the urine was negative and this on catheterized urine. We believe, therefore, that this case indicates a purely functional (as contrasted to the previous case) renal impairment which raised the threshold of ketone body elimination. Dehydration, as shown by the refractometric examination of the blood, and low blood pressure, no doubt, contributed to this functional renal disability. The conductivity measurements (Table Va) indicate that the plasma base was somewhat below normal.

Joslin²³ says that "the simplest method for the detection of acidosis by urinary examination is Gerhard's ferric-chlorid reaction for diacetic acid."

This test is used, no doubt, by the majority of physicians and patients for the detection of acid poisoning. Certainly diacetic acid usually increases in the urine when coma approaches and Hurtley²⁴ states that "the ratio of aceto-acetic to hydroxybutyric acid in the urine increases with the severity of the intoxication."

Case V in our series did not show a positive ferric-chlorid reaction

on entry and yet she died in less than thirty-six hours without ever showing this reaction. The point should be made, therefore, that an absent ferric-chlorid reaction does not preclude the diagnosis of threatened diabetic coma and if a diabetic is feeling ill it is unwise for him not to call a physician because the urine does not give a positive ferric-chlorid reaction.

The ferric-chlorid reaction in the second place is frequently used as an indication of the progress made in the treatment of a case of diabetic coma. One usually concludes that when the ferric-chlorid reaction becomes negative in the urine, that the case is under good control. As we have seen, our cases have shown at one time or other in the course of the disease a degree of acidosis as indicated by the CO_2 content of the plasma which we should not have supposed to exist from the ferric-chlorid test in the urine. One cannot relax one's efforts at treatment, therefore, when the ferric-chlorid reaction first becomes negative in the urine.

We have not discussed the possibility of an unusually rapid decomposition of diacetic acid into acetone in the urine. We have merely made certain observations. Many of our urine analyses were made on catheterized specimens and were repeatedly checked, so that if a transformation took place, it must have occurred in the bladder. Wells²⁵ quotes Folin as saying that fresh diabetic urine does not contain acetone and that when a test for the latter is obtained it is due to the decomposition of diacetic acid. The only way we could have obtained fresher urine would have been by ureteral catheterization.

Clinically, however, our fresh diabetic urine showed positive reactions for acetone. We used, however, the sodium nitroprusside reaction and Folin²⁶ says that the acetone tests used by clinicians are really tests for diacetic acid. The nitroprusside reaction Mathews²⁷ and Folin (*ibid.*) point out, is much more sensitive for diacetic acid than the ferric-chlorid reaction. The former being sensitive to one part in 30,000; while the latter is sensitive only to one part in 7000. Clinicians have usually spoken of the one as being a test for acetone and the other for diacetic acid. It appears, therefore, that they have not been correct in this and that the point of the tests has been in the significance of the *amount* of diacetic acid in the urine as an indication of acid intoxication.

Conclusions. An absent ferric-chlorid reaction in the urine:

1. Does not preclude the diagnosis of threatened diabetic coma.
2. In a case of diabetic coma under treatment does not always mean that the case is well under control.
3. Does not mean necessarily that the plasma CO_2 content is out of the acidotic range.
4. Cannot be taken to indicate that the blood ketones are not greatly increased.

5. As an explanation of an absent ferric-chlorid reaction in the urine in threatened diabetic coma, in advanced diabetic coma under treatment, in diabetic coma with a low CO_2 , in diabetic coma with considerably increased blood ketones, we suggest that the absence is probably due to temporary renal impairment usually on a basis of dehydration.

APPENDIX I. Methods used in making determinations.

Urinary sugar was tested both by Benedict's and Fehling's methods.²⁶

Urinary acetone and diacetic acid were tested by the usual sodium nitroprusside + ammonia, and ferric-chlorid, reactions respectively.²⁶

Blood sugar and urea-nitrogen determinations were made by Folin's method.²⁶

Blood plasma carbon-dioxid content was determined by the van Slyke method.²⁸

Blood-acetone determinations were made by van Slyke's method.²⁹

Total base was determined by the method of Stadie and Ross.³⁰

Plasma chlorids were determined by the method of van Slyke.³¹

Freezing-point determinations were made by the cryoscopic method of Burian and Drucker.³²

Ionometric measurements were made by the ionometer as described by Christiansen³³ and corrections were made for the protein content of the plasma.³⁴

Phenolsulphonophthalein determinations were done by the intravenous method.

Food calculations were made by the hospital dietitian.

For composition and physical properties of human blood see Gram's article.³⁵

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HYPOGLYCEMIA.

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THE question of the existence of a chronic condition of hypoglycemia has been brought to the fore by our experiences with insulin and by the observations of such men as Seale Harris.¹

It has seemed to us probable that some light could be thrown on the question by studying the records of routine blood sugar

tolerance tests, and, whenever a hypoglycemic condition was discovered, noting the symptomatology presented by those patients. This would, of course, demand that we establish a low limit for the normal. It would demand also that all those cases of hypoglycemia where the results are dependent on complicating circumstances (such as pylorospasm) be ruled out. And further it would require a study of the curves in order to see if the hypoglycemic curve presented the same type of curve as the normal curve.

We have, therefore, gone over our records of routine examinations and find that of 307 examinations made, there were many cases showing low blood-sugar levels, and that among these were curves that were as truly diabetic in form as among the hyperglycemics, and also (that which was for the most part present) there were strictly normal curves. We have, therefore, proceeded with the study and submit the following notations:

Method of Study. When the study of blood sugar was introduced, we used the Epstein micro method. Then as the technique was better refined, we used the picric-acid method of Benedict, and finally the technique of Folin and Wu. The results obtained by these three methods were so uniform, that we believe our records are comparable and correct.

The tests for sugar in the urine were all made with Benedict's qualitative solution.

Our routine method was to have the patient come to the office in the morning, fasting. After the urine and blood were taken, syrupy glucose was given in doses of 1.75 gm. per kilogram of body weight, made up to the quantity of 300 cc. by the addition of water and the juice of one orange. Reëxamination of the blood and urine was made at the end of a half hour, at the end of the hour, and at the end of two hours. We have found that the curve, at the end of two hours, was sufficiently definite to give us a clew as to whether it was diabetic or not. Consequently we have omitted taking the blood and urine at the third and fourth hours.

In collecting the cases for this study, we have set as the lower limit for the normal at 0.07, for the fasting condition; and the high point at 0.12, in order to eliminate those cases in which the blood-sugar level was only temporarily low, and which under ordinary conditions would rise higher.

We might say also that many, if not most, of these patients were submitted to this study, not because they were suspected of being diabetic, but in order to evaluate their endocrine balance, in particular with the study of the basal metabolic rate. In this way, we have obtained a different group than if we had studied only those who were suspected of being diabetic.

Results. Of 307 routine studies, 95 had a fasting blood sugar below 0.07, and of these 95, 50 showed a curve that did not rise above 0.12. It is worth noting that there were 23 cases that had a

blood sugar below 0.07 in which sugar appeared in the urine during the test. This may be taken as corroborative evidence of the independence of the blood sugar level from glycosuria.

As soon as we began to study the symptoms presented by this group of 50 cases, we found it wise to separate them into two sub-groups—those with mental disturbances and those without. Perhaps this was unnecessary but it gave us a further subdivision of the groups. We made further a subdivision between those showing glycosuria and those not showing glycosuria. As a result, we

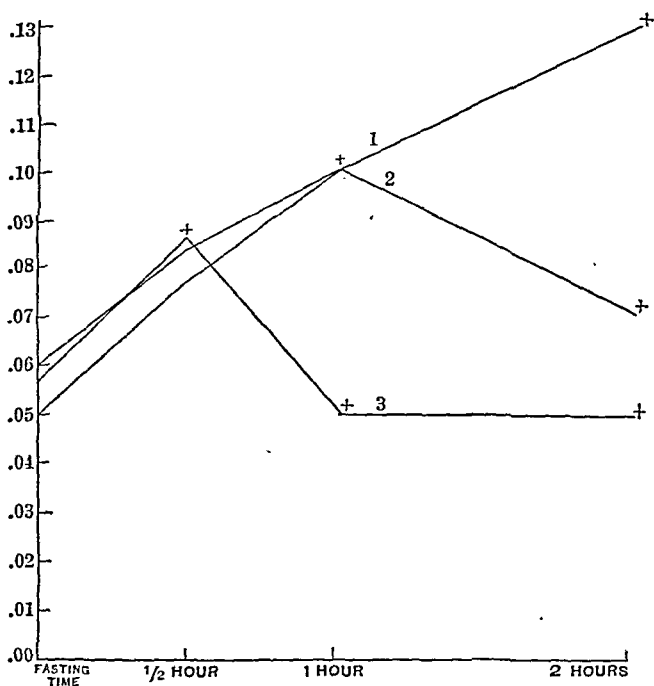


FIG. 1

divided the cases into four groups: Group I, hypoglycemia with glycosuria and showing mental disturbance; Group II, hypoglycemia with glycosuria but without distinct mental disturbance; Group III, hypoglycemia without glycosuria and without mental disturbance; Group IV, hypoglycemia without glycosuria but with mental disturbance.

Under Group I, that is, patients with hypoglycemia and glycosuria, who show distinct mental disturbance—we found only three patients who conformed to the limits of the test. These were a girl, nineteen, a woman, thirty-eight, and a woman, fifty-one years of age (Fig. 1).

The girl exhibited symptoms of duodenal ulcer but was mentally so ill-balanced that she would not take any consecutive line of treatment. At the time of first examination, her blood pressure was 80 to 122; temperature, 98.4; pulse, 88. The symptoms began with influenza in 1919 which had been followed by a cough

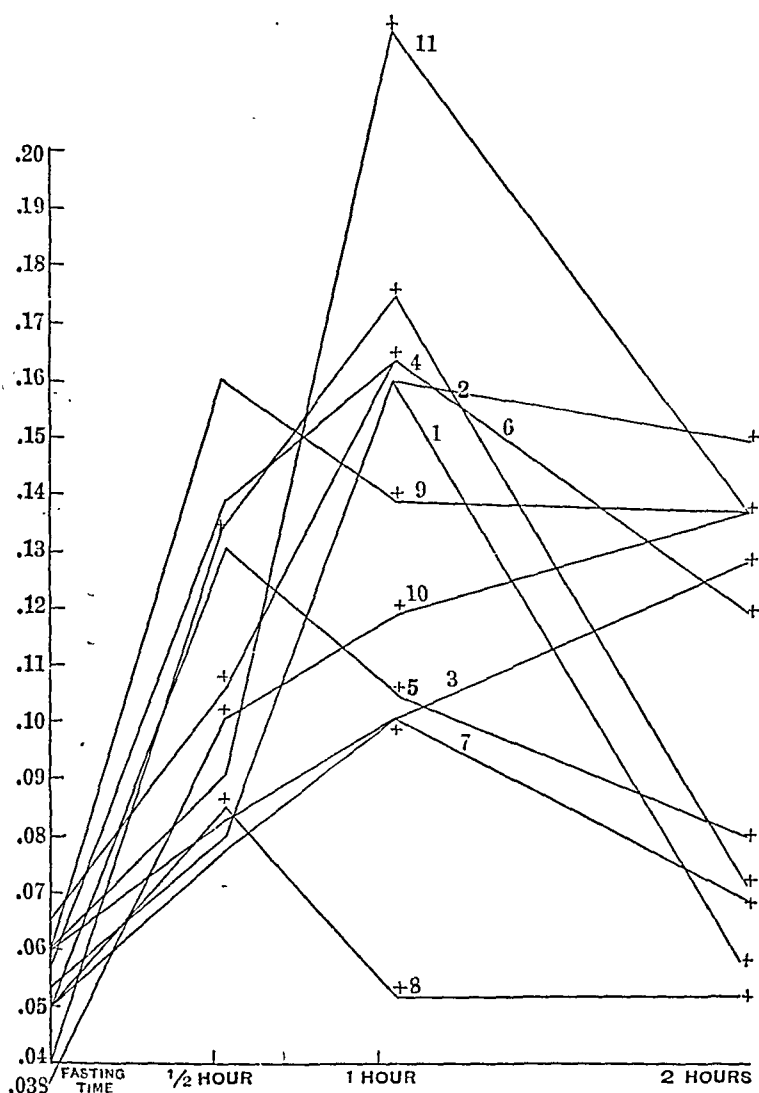


FIG. 2

with soreness of "stomach." The soreness of the abdomen kept her awake. Appetite poor. Bowels constipated. Menstruation normal. The Roentgen ray examination showed a distorted duodenum with considerable dilatation. She was jumpy both physically and mentally.

No. 2 complained chiefly of pain in the lower right abdomen, of flatulence, loose bowel action, poor appetite, poor sleep, irregular

menstruation. At the time of her first examination her blood pressure was 90 to 140; temperature, 99; pulse, 100. Her best weight had been 154 and was then 141. There was a trace of sugar in the urine. The culture of the urine showed colon bacillus infection. Her weakness was such that she could not care for her children, and was unable to see anything but the dark side of life. Nevertheless, during the period of observation she gave birth to a healthy child.

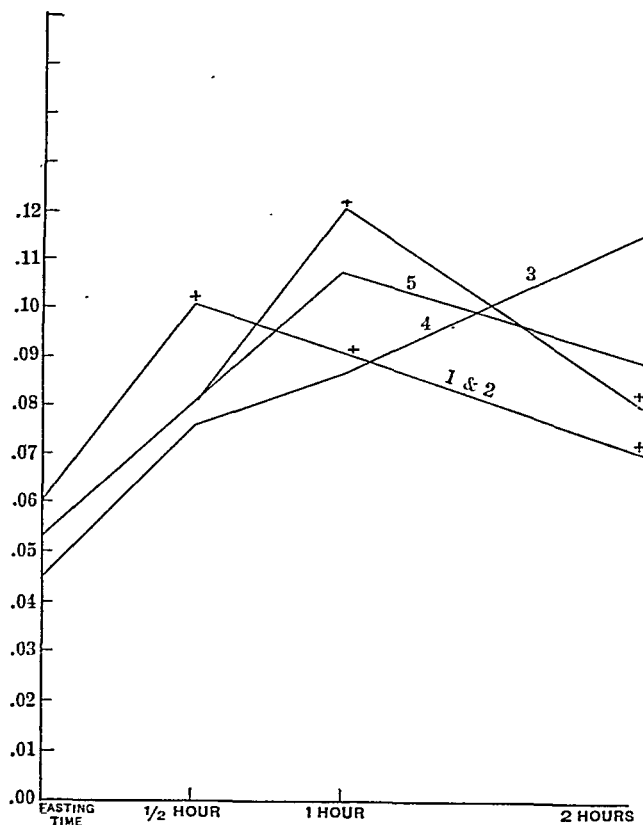


FIG. 3

No. 3 complained of various abdominal pains and nervousness. Her temperature was 99.3, pulse, 112. Best weight 180, present weight 171 pounds. The phthalein renal-function test was 41 per cent in two hours, and the urine showed occasional traces of sugar. She was particularly apprehensive and rather exaggerated every possibility of misfortune.

If we were to enlarge this group by including in it those cases wherein the blood-sugar level went high during the test, we should

have 11 cases but the symptomatology would not vary greatly from that which we have just reviewed (Fig. 2).

Under Group II, that is, those showing hypoglycemia with glycosuria but without distinct mental disturbance, we found 5 cases. No. 1, was a girl, aged nineteen years, who had been compelled to begin work for a living and became thoroughly exhausted in the struggle for existence. No. 2, was a university student who

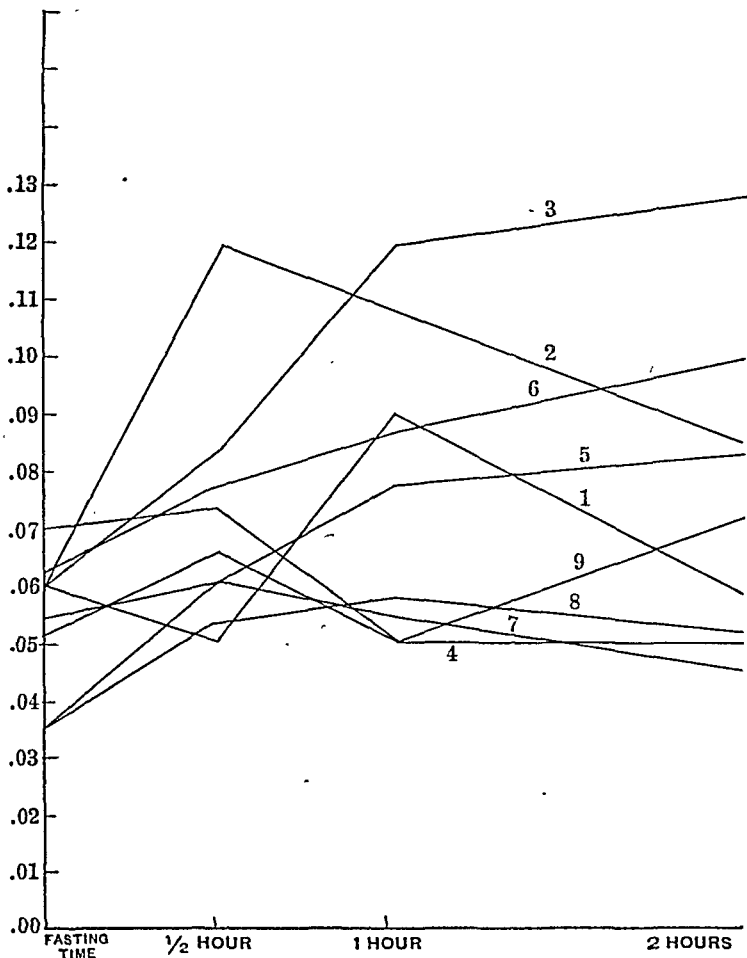


FIG. 4

had influenza followed by an inflammation apparently perisplenic in reaction. No. 3 was a deaf man, aged thirty-five years, with Graves' disease. No. 4 was a deaf man, aged sixty years, irritable and finding it difficult to make both ends meet. No. 5 was a pregnant woman, aged thirty-nine years. The complaints of these people included sick headaches, pain in the chest, nausea and vomiting. The young girl fainted at work and suffered from cardiac palpitation (Fig. 3).

There were 9 cases in Group III, that is, hypoglycemia without glycosuria and without mental disturbance. No. 1 was that of an incipient tuberculosis in an overworked journalist; No. 2, an obese nurse; No. 3, a young woman with incipient tuberculosis; No. 4, an overworked musician; No. 5, a teacher with chronic arthritis; No. 6, an overworked young law student; No. 7, an overworked librarian; No. 8, was a bank teller who had influenza one year

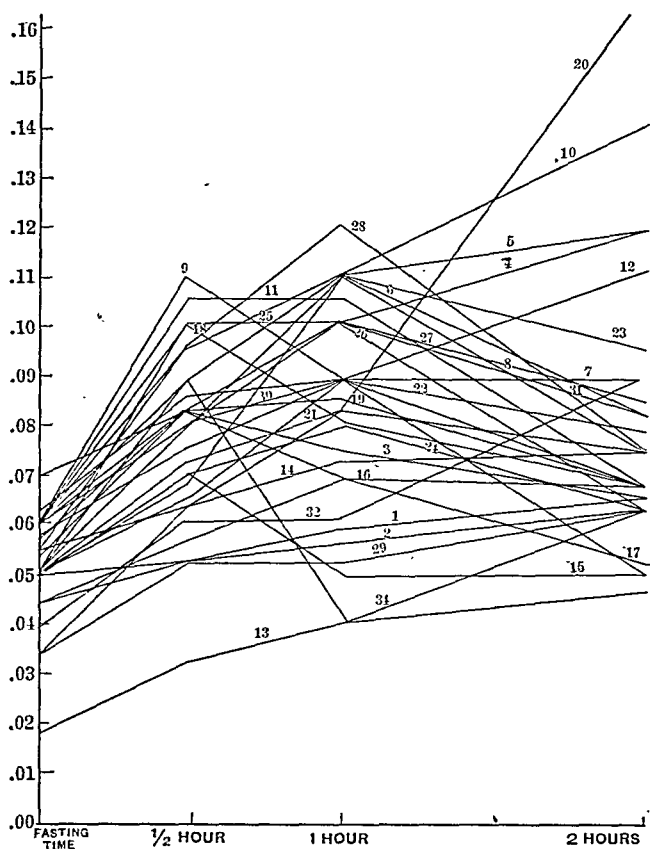


FIG. 5

previous; No. 9 was an overworked Y. W. C. A. secretary. The general symptoms were fatigue, nervousness, depression, and in the young women, attacks of weeping and the general complaint of dysmenorrhea (Fig. 4).

There were 33 cases in Group IV, that is, hypoglycemia without glycosuria but with some mental upset. They might all be grouped under the head of constitutional inferiority, or, again, the disciple of Freud would find in them all sorts of complexes. Here again

there was among the women the complaint of irregular menstruation, backache, headache, fatigue, lack of endurance and even of abdominal pain. The males complained chiefly of inability to keep up with their fellows in one or more particulars, with the exception of a boy, aged fourteen years, who had distinct epileptiform attacks (Fig. 5).

Comment. The perusal of these sketchy notes on the case histories hardly leaves the reader with an adequate idea of the conditions involved or the symptoms presented, therefore we think that it may be worth while to give our own opinion as to the significance of this group of cases.

There is apparently a condition in which the blood stream contains an amount of sugar less than that spoken of as normal. This condition can exist for considerable time, that is, become chronic. Furthermore this condition seems to be accompanied by nervous and mental disturbances very much akin to those presented by the initial symptoms of acute hyperinsulinism or hypoglycemia.

As far as one could judge from the study of these cases the cause does not lie in a lesion of the pancreas, rather it seems to lie in a general depression of the metabolism of the body.

But it is not clear from these case histories whether the hypoglycemia is the cause of the nervous disturbance or *vice versa*. But since we have noticed that the hypoglycemia tends to disappear as soon as the general nutrition of the patient improves, we have been led to think that the hypoglycemia is a result of the general nervous state rather than the cause of it.

If we accept the opinion of Falta and others that in disordered sugar metabolism and diabetes there is involved more than a lesion of the pancreas—that there is a disorganization of the vegetative nervous system—then it is easy to understand that in our cases the hypoglycemia may result from a disorganization of the nervous system rather than from any lesion of the pancreas or from hyperinsulinism. Furthermore, as far as we can ascertain from a perusal of these histories the metabolism seems to be slowed down rather than stimulated. In other words, it is not hyperinsulinism so much as a lowered sugar metabolism.

This study emphasizes again the mutual independence of glycosuria and the blood-sugar level. A glance at the curves show the percentage of diabetic curves is about that which one would expect from an unselected run of office cases.

The underlying cause of the condition seems to have been overwork, debilitating disease (such as influenza), and worries. In other words, some type of exhaustion. Focal infection was, of course, occasionally present; but focal infection is just one of the causes of systemic exhaustion.

The effect of treatment in this group of cases is marked. We have been able to watch the blood-sugar reaction in several of the

cases listed in this communication and have found that with the returning strength the blood sugar returned to its normal limits. This usually occurs in from three to six months. This result would indicate that the theory that this hypoglycemia reaction is due to exhaustion is the correct one.

As to the type of treatment we have found that arsenic, introduced in the form of arsacetin or even of the cacodylates, or occasionally in the form of silver-salvarsan has been most effective. This was of course combined with synergistic symptomatic treatment.

REFERENCE.

1. J. Am. Med. Assn., 1924, 83, 729.

A CONFIRMATORY SIGN FOR THE DIAGNOSIS OF OTITIS MEDIA ASSOCIATED WITH PULMONARY TUBERCULOSIS.

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PATIENTS with pulmonary tuberculosis who have otitis media are able to perceive with the diseased ear, sounds originating in their respiratory tract. They are oftened puzzled over this apparent paradoxical phenomenon of hearing only with their "deaf" ear such intrathoracic sounds as rales, rhonchi and squeaks. These sounds can be differentiated by oral auscultation from the subjective sensations of buzzing, ringing or pulsations, usually complained of in otitis media. In every instance of otitis media rales originating in the tuberculous lung, when detected by the examiner orally, were also heard by the diseased ear, and when such oral auscultation was negative no rales were heard by the patient.

We can utilize this clinical picture as a confirmatory sign in the diagnosis of otitis media in phthisical patients. We believe it is important in such cases and should be used along with the routine otologic tests. In every instance it was confirmed by the Weber, Schwabach, Rinne and whispered-voice tests. It indicated the presence of an involvement of the sound-conducting mechanism of the diseased ear and served to differentiate such disturbance from nerve deafness.

The following cases illustrate its diagnostic value:

CASE I.—(No. 8350.) A man, aged forty years, in November, 1924, had a spontaneous discharge from the right ear, without pain

or fever but with concomitant loss of hearing. The discharge lasted about six months. Since then there has been a constant ringing in this ear. For the past year he has also heard with the right ear a crackling, clicking sound which comes from his throat and chest only when he breathes, both on inspiration and expiration.

Otologic examination showed a central perforation of right tympanic membrane, but no discharge.

Hearing tests: (a) Whispered voice: Left: Normal. Right: Low-pitched words (five, nine and so forth) heard at a distance of $1\frac{1}{2}$ inches; high-pitched words (six, seven and so forth) heard at a distance of 2 inches.

(b) Weber: Right: Tuning fork C (128 vibrations per second), positive.

(c) Schwabach: Right: Tuning fork C, positive ten seconds.

(d) Rinné: Right: Tuning fork C, negative twelve seconds; C¹ (256), negative ten seconds; C² (512), negative twenty seconds; C³ (1024), negative twelve seconds.

Diagnosis: Right chronic otitis media sicca.

Oral auscultation: Constant, large, moist rales.

Physical examination of the lungs: Fibroulcerative tuberculosis involving the entire left side and the right upper lobe with scattered infiltrations throughout the right middle and lower lobes. There is a large cavity in the right upper lobe and a small cavity in the left upper lobe. Numerous large and small moist rales are heard over both lung fields.

CASE II.—(No. 8173.) A man, aged twenty-one years, in May, 1924, had a "cold in the head." He felt a slight pain in his right ear associated with a ringing sound. Three days later he noticed a yellowish-brown discharge from this ear which persisted. The hearing gradually decreased. His diseased ear now conveys the sensation of clicking and rasping sounds which originate in his throat and chest. These superimposed sounds are only present when the patient breathes.

Otologic examination showed destruction of the entire right tympanic membrane, with a thin, purulent discharge.

Hearing tests: (a) Whispered voice: Left: Normal. Right: Low-pitched words (five, nine, and so forth) heard at a distance of 5 to 7 inches; high-pitched words (six, seven and so forth) heard at a distance of 11 feet.

(b) Weber: Right: Tuning fork C, positive.

(c) Schwabach: Right: Tuning fork C, positive eight seconds.

(d) Rinné: Right: Tuning fork C, negative fourteen seconds; C¹, negative ten seconds; C², negative twelve seconds; C³, negative fifteen seconds.

Diagnosis: Right chronic purulent otitis media.

Oral auscultation: Constant, large, moist rales.

Physical examination of lungs: Bilateral fibroulcerative tuberculosis with a large cavity in the left upper lobe and a small cavity in the right upper lobe. Large constant moist rales over both upper lobes.

CASE III.—(No. 8350.) A man, aged twenty-seven years, in January, 1925, had severe pains in the left ear which radiated to his head. This pain subsided five weeks later, when a thin yellowish discharge appeared. The hearing was lost at this time. The discharge has been continuous. He has a constant ringing and buzzing in this ear; but during the past few months on inspiration only, he also hears a faint clicking sound which comes from his throat and chest.

Otologic examination showed destruction of three-fourths of the tympanic membrane of the left ear, with a thin, purulent discharge.

• Hearing tests: (a) Whispered voice: Right: Normal. Left: Low-pitched words (five, nine and so forth), no perception; high-pitched words (six, seven and so forth) heard at a distance of 3 inches.

(b) Weber: Left: Tuning fork C, positive.

(c) Schwabach: Left: Tuning fork C, positive eleven seconds.

(d) Rinné: Left: Tuning fork C, negative twenty-seven seconds (no air conduction); C¹, negative sixteen seconds (no air conduction); C², negative forty seconds; C³, negative twenty-eight seconds.

Diagnosis: Left chronic purulent otitis media.

Oral auscultation: Distant, small, moist rales.

Physical examination of lungs: Fibroulcerative tuberculosis of both upper lobes. Numerous constant large and small moist rales in these areas.

The next case is cited as a contrast:

CASE IV.—(No. 8294.) A man, aged twenty years, about 1918, had a thin, yellowish discharge from the right ear associated with no pain or impairment of hearing. The patient did not consider himself sick at that time. The discharge ceased after a year. In March, 1926, the right ear again began to discharge, soon followed by impairment of hearing without pain. He has a constant ringing sensation in the diseased ear, but hears no sounds emanating from throat or chest.

Otologic examination showed that the upper and lower anterior quadrants of the right tympanic membrane were destroyed, with a thin purulent discharge.

Hearing tests: (a) Whispered voice: Left: Normal. Right: Low-pitched words (five, nine and so forth) heard at a distance of 1½ inches; high-pitched words (six, seven and so forth) heard at a distance of 2 feet.

(b) Weber: Right: Tuning fork C, positive.

(c) Schwabach: Right: Tuning fork C, positive twenty seconds.

(d) Rinné: Right: Tuning fork C, negative twenty-five seconds; C¹, negative twelve seconds; C², negative thirty-six seconds; C³, negative fifteen seconds.

Diagnosis: Right chronic purulent otitis media.

Oral auscultation: Negative.

Physical examination of lungs: Fibroulcerative tuberculosis of right upper and middle lobes with small cavity in left upper lobe. Numerous fine, constant, moist rales over these areas.

The following case demonstrates the differential diagnostic significance:

CASE V.—(No. 7734.) A man, aged twenty-seven years, claims that he was born deaf. He has an occasional "ringing" sensation in his ears, but hears no sounds from his throat or chest.

Otologic examination showed a retraction of both tympanic membranes. The left is atrophic and transparent. The manubrium mallei and the promontorium are distinctly visible.

Hearing tests: Rinné: Positive. The only tone perceived was C⁴ by air conduction: Ten seconds on the right and twelve seconds on the left.

Diagnosis: Congenital acoustic nerve disease.

Oral auscultation: Constant, large, bubbling rales.

Physical examination of lungs: Bilateral fibrocavernous tuberculous lesion of upper lobes with ulcerative process throughout the left lower lobe. Large, constant moist rales.

Summary. The first 3 cases present unilateral chronic purulent otitis media. In each instance the rales heard over the diseased lung were audible by oral auscultation as well. The patient heard these rales only with the diseased ear. The fourth case also shows a chronic purulent otitis media. The rales present in the chest were not heard by oral examination nor were they heard by the patient. The fifth patient has congenital nerve deafness. Bubbling rales heard orally and by thoracic examination were not heard by the patient.

What is the mechanism of transmission and perception of these rales? In otitis media, as is well known, there is impaired air conduction and intensified bone conduction on the diseased side. In the first 3 cases cited the rales detected by oral auscultation were conveyed from the lung to the trachea. From here they were transmitted to the bones of the head, and because of the better bone conduction were heard by the diseased ear. In Case IV there was no transmission of the rales from the lungs to the oral cavity and hence they could not be appreciated by the patient. In the

case of the nerve deafness, while the rales were conveyed to the oral cavity and to the cranial bones; they were not perceived by the patient because in nerve deafness there is a lack of nerve response to most sound waves; only a few extremely loud tones can be heard.

Conclusions. Tuberculous patients with otitis media often can hear their pulmonary rales with their diseased ear. This audition of pathologic sounds serves to differentiate otitis media from acoustic nerve involvement.

THE EFFECT OF BISMUTH ALONE AND IN COMBINATION WITH THE ARSENOBENZENES ON THE WASSERMANN REACTION.¹

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THAT bismuth exerts a favorable action on the course of syphilis is well known and generally accepted at the present date. Given intramuscularly its action is equal to if not superior to that of mercury and the day is approaching when bismuth will perhaps largely replace mercury in the treatment of syphilis, as it is therapeutically stronger, less painful and less toxic.

The day of sole dependence on the arsenobenzenes has passed. With but few exceptions, syphilographers now agree that adjunctive treatment is not only desirable but is imperative. It is the writer's purpose in this paper to indicate the value of bismuth as an adjunct to the arsenobenzenes.

Before 1922 it was the custom in the syphilis clinic of the Polyclinic Hospital in Philadelphia,² to treat all stages of syphilis with long courses of neoarsphenamin, mercury being reserved for such cases as were intolerant or resistant to the arsenobenzenes, and for short rest periods. With the introduction of bismuth this procedure was changed and treatment by means of alternate courses of neoarsphenamin and bismuth was instituted in new cases and to those patients who had had a considerable amount of arsenobenzen treatment previously, bismuth alone was given. Since 1923, the writer has personally administered the intramuscular treatment to over 200 cases, in all giving between 4000 and 5000 injections of the drug. Of these cases, 160 received a sufficient amount of treatment to enable the drawing of some conclusions as to the

¹ Potassium bismuth tartrate furnished by the Dermatological Research Laboratories.

² Clinic of Prof. Jay F. Schamberg.

effectiveness of the treatment. Courses of injections were given, 16 injections being the usual number for a course but in some instances as many as 30 or 40 consecutive treatments were administered, at weekly intervals. Potassium bismuth tartrate was used in doses of 100 mg. each week. This dose was decided upon because it kept the patient just at the saturation point, as evidenced by the presence of a blue line on the gums after three or four weeks of treatment.

Potassium Bismuth Tartrate as an Adjunct to Neoarsphenamin in Secondary Syphilis. Owing to the segregation of cases of secondary syphilis in the clinic for other therapeutic research, only 10 cases have received the usual neoarsphenamin followed by bismuth. It was formerly a routine in the clinic to give from 10 to 20 injections of neoarsphenamin for the first course of treatment of secondary syphilis, the average dose being 0.6 gm. weekly for women and 0.9 gm. for men. After a short rest period, neoarsphenamin was again given. Thus it will be noticed in Table I that one patient received as many as 50 injections of neoarsphenamin before bismuth was given. It is of further interest that this patient was still serologically positive after this number of injections and became Wassermann negative after 18 injections of bismuth or a total of 1.8 gm. of the drug. Of the 10 cases in this series, 6 were serologically negative after an average of 11 injections of neoarsphenamin. All of these have remained persistently negative under further intramuscular injections of bismuth. Each of the 4 cases which were still Wassermann positive after the first course of neoarsphenamin, became negative after an average of 10 injections of bismuth, and to date have remained persistently negative.

Bismuth as an Adjunct to Neoarsphenamin in the Treatment of Secondary Syphilis. In all, 75 cases of syphilis having no other symptoms than a positive blood Wassermann reaction received a sufficient amount of bismuth to draw some conclusions as to its value. Of these 75 cases, only 18 (or 22.5 per cent), were serologically negative after an average treatment of 17 injections of neoarsphenamin and 7 injections of mercury (insoluble). With the institution of bismuth there remained 57 cases having a positive blood Wassermann. Of these 57 cases, 32 (or 51 per cent) became serologically negative after an average of 13 injections of bismuth. It is interesting to note that all of the 18 cases which were Wassermann negative after treatment with neoarsphenamin and mercury have remained negative under subsequent bismuth therapy. Of the 32 cases which became negative after the institution of bismuth all but 5 have remained serologically negative. The 5 cases which again became Wassermann positive took self-advised rest periods varying from several months to a year, during which time they received no treatment at all.

TABLE I.—SECONDARY SYPHILIS TREATED WITH NEOARSPHENAMIN AND SUBSEQUENTLY WITH BISMUTH.

Name.	Neoarsphenamin, doses.	Wassermann after neoarsphenamin.	Bismuth, doses.	Wassermann after bismuth.	Wassermann reaction became negative.
M. Br.	16	Neg.	16	Neg.	After 9 injections neoarsphenamin.
M. Bo.	50	4+	44	Neg.	After 18 injections bismuth.
B. D.	16	Neg.	16	Neg.	After 7 injections neoarsphenamin.
M. F.	18	4+	38	Neg.	After 10 injections bismuth.
J. K.	10	4+	28	Neg.	After 6 injections bismuth.
C. K.	10	4+	43	Neg.	After 8 injections bismuth.
M. M.	14	Neg.	14	Neg.	After 9 injections neoarsphenamin.
A. M.	20	Neg.	43	Neg.	After 18 injections neoarsphenamin.
F. L.	18	Neg.	22	Neg.	After 16 injections neoarsphenamin.
D. S.	18	Neg.	60	Neg.	After 10 injections neoarsphenamin.

Certain cases in this group are of particular interest:

CASE I.—A. C., female, colored, aged thirty years, presented no symptoms of syphilis other than a positive Wassermann reaction, and received a total of 28 injections of neoarsphenamin (average dose, 0.6 gm. weekly) over a period of one and a half years. At the end of that time the Wassermann reaction was negative. After a short rest period, the Wassermann was again strongly positive. Bismuth was then started and after 6 injections of 100 mg. each of the drug, the blood Wassermann was again negative and has remained so for two years during which time the patient has had two healthy nonsyphilitic children.

CASE II.—G. G., female, white, aged twenty-eight years, presenting no signs or symptoms of syphilis other than a strongly positive Wassermann reaction, received 16 injections of neoarsphenamin after which the Wassermann was still strongly positive. After 14 injections of bismuth (100 mg. each) the Wassermann reaction was negative. Treatment with neoarsphenamin was then again instituted and while receiving this drug the blood Wassermann again became positive. She is now receiving bismuth again.

CASE III.—G. W., colored, male, aged twenty-eight years, with no evidence of syphilis other than a strongly positive Wassermann reaction, received 20 injections of neoarsphenamin (average dose, 7.5 gr. weekly), then 14 injections of 2 gr. each of the mercury salicylate intramuscularly. This was followed by a second course

of neoarsphenamin consisting of 20 injections. After all of this treatment, the Wassermann reaction was still strongly positive. Bismuth was then instituted and 16 injections of the drug have reduced the Wassermann reaction to negative.

Use of Potassium Bismuth Tartrate as Adjunctive Treatment in Tertiary Syphilis. It is well known that it is extremely difficult to influence the Wassermann reaction in cases of cutaneous, visceral or nervous system tertiary syphilis with any kind or amount of therapy. Including all these three types, 27 cases of tertiary syphilis were treated, all of which were serologically positive in the beginning and only 2 of which were negative at the start of bismuth therapy. After an average of 16 injections of bismuth, 7 of the 25 still Wassermann positive cases were serologically negative. Four of these later reverted to positive. In these cases bismuth apparently does not exert a more favorable influence upon the blood Wassermann than do other antisiphilitic remedies.

Use of Bismuth in Congenital Syphilis as Adjunctive Treatment to Neoarsphenamin and Mercury. Upon the suggestion of Dr. Schamberg, a number of cases of secondary and latent syphilis were treated with alternate injections of neoarsphenamin and bismuth, one injection of each drug being given in the same week, at intervals of three days, the usual doses being employed. The efficacy of this therapeutic procedure may be ascertained by a study of Tables II and VI.

1. *Secondary Syphilis.* In all, 13 cases of secondary syphilis have been treated in this manner to date. All of these were serologically negative before the completion of the first series of injections covering a period of twelve weeks. The average number of weeks required to obtain negative serologic reactions was six. In 1 case, a colored girl with a maculopapular eruption and rectal condylomata, the Wassermann reaction was negative after three weeks. In secondary syphilis treated in this way it has been customary to give first an injection of 100 mg. of potassium tartrobismuthate, in order to avoid the danger of a Herxheimer reaction, or toxic reaction so often caused by initial injection of neoarsphenamin intravenously. So successful was this treatment in this number of cases that it is advised for all cases of early syphilis. It is of further importance that in not one of these cases reported has the Wassermann reaction reverted to a positive. The effect upon the local manifestations of syphilis is magical. Under the combined influence of bismuth and neoarsphenamin cutaneous lesions disappear with astonishing rapidity.

TABLE II.—TERTIARY SYPHILIS TREATED WITH NEOARSPHENAMIN AND SUBSEQUENTLY WITH BISMUTH.

Name.	Diagnosis.	Previous therapy.		Wassermann at start of bismuth.	Doses of bismuth to date.	Doses of bismuth for negative Wassermann.	Wassermann not affected.
		Neoarsphenamin, doses.	Mercury, doses.				
M. B.	Aortitis	9	?	4+	28	...	Wk. pos.
C. B.	Gummata	25	8	Wk. pos.	20	12	
L. B.	Tabes	Wk. pos.	40	12	
E. B.	Tabes	4+	30	...	+
H. B.	Tabes	128	32	4+	28	24	
P. C.	Tabes	10	...	4+	32	...	+
H. C.	Gumma	4+	24	...	+
I. C.	C.S.S.	35	16	4+	75	...	+
A. C.	Tabes	38	9	4+	10	...	+
M. F.	Gumma	51	18	4+	45	...	+
A. F.	Gumma	20	...	4+	53	16	
W. F.	Gumma	28	14	4+	30	19	
C. G.	C.S.S.	8	...	4+	36	...	+
M. H.	Gumma	12	...	Neg.	24	...	*
M. K.	Gumma	30	?	4+	33	...	+
E. H.	Gumma	24	10	4+	12	...	+
E. M.	C.S.S.	2	...	2+	71	16	
I. P.	Gumma	14	...	+
A. P.	Gumma	18	...	4+	22	...	+
U. P.	Gumma	4+	16	16	
B. R.	Tabes	13	...	4+	20	...	+
M. S.	Optic atrophy	4+	28	...	+
C. S.	Optic atrophy	20	12	4+	34	...	+
P. T.	C.S.S.	17	6	4+	26	...	+
H. T.	Aneurysm	26	11	Neg.	30	...	*
H. V.	Tabes	52	17	4+	40	...	+
C. W.	C.S.S.	16	...	4+	26	...	+

* Wassermann persistently negative.

TABLE III.—CONGENITAL SYPHILIS TREATED WITH NEOARSPHENAMIN AND SUBSEQUENTLY WITH BISMUTH.

Name.	Other therapy.		Wassermann at start of bismuth.	Doses of bismuth to date	Doses of bismuth to render Wassermann negative.	Uninfluenced.
	Neoarsphenamin.	Bismuth.				
M. B.	40	18	4+	60	27	
B. B.	12	...	4+	50	20	
A. B.	Mod. pos.	25	...	+
I. B.	16	...	4+	40	...	+
G. C.	30	9	4+	20	...	+
V. C.	51	13	4+	45	...	+
R. D.	38	16	4+	60	16	
H. D.	15	...	4+	30	28	
M. G.	51	16	4+	45	...	+
H. G.	16	...	4+	44	7	
A. H.	17	...	2+	12	12	
E. K.	50	22	4+	50	88	
F. M.	8	...	4+	30	18	
E. M.	38	14	4+	63	...	+
S. P.	21	...	4+	28	...	+
B. V.	4+	28	18	

TABLE IV.—SECONDARY SYPHILIS TREATED WITH ONE INJECTION OF NEOARSPHENAMIN AND ONE INJECTION OF BISMUTH WEEKLY.

Name.	Eruption.	Weeks to obtain negative Wassermann.	Remarks.
E. B.	Maculopapular condylomas	3	Rapid disappearance of lesions.
A. D.	Papular, moist papules	9	
R. M.	Maculopapular	4	Has remained negative under further bismuth therapy.
M. J.	Roseola, moist papules	12	No Wassermann taken until completion of the first course.
L. M.	Maculopapular	8	Has remained negative under further bismuth therapy.
G. S.	Maculopapular	6	Has remained persistently negative under further bismuth therapy.
W. S.	Maculopapular	5	Has remained negative under further bismuth therapy.
B. E.	Roseola	9	Has remained negative.
C. M.	Maculopapular	4	Still negative some months later; disappeared then from clinic.
H. W.	Maculopapular	5	Rapid involutions of the eruption.
D. W.	Maculopapular moist papules	5	Has remained persistently negative.
P. T.	Maculopapular	5	Has remained persistently negative.
D. W.	Maculopapular	...	Has remained persistently negative.
Dr. M.	Roseola	6	Has remained persistently negative.

TABLE V.—LATENT SYPHILIS TREATED WITH ONE INJECTION OF NEOARSPHENAMIN AND ONE INJECTION OF BISMUTH WEEKLY.

Name.	Wassermann.	Weeks to obtain a negative.	Wassermann reverted to positive.	Wassermann uninfluenced.
N. B.	4+	5	+	
P. B.	2+	7		
G. D.	4+	+
N. C.	4+	5		
A. E.	4+	9		
A. L.	1+	6		
A. M.	4+	12		
M. F.	4+	6		
B. J.	4+	12	+	
M. R.	4+	5		
J. G.	4+	8		
G. W.	4+	+
W. W.	4+	+
M. W.	4+	8		
J. W.	4+	5		
R. W.	4+	+
M. P.	4+	6		
J. M.	4+	6	+	

TABLE VI.—SUMMARY OF RESULTS.

	Diagnosis.					
	Secondary lucs.	Latent lucs.	Tertiary lucs, cutaneous	S. S. C. Tertiary lucs.	Secondary visceral lucs.	Hereditary lucs.
Number of cases	9	75	11	14	3	16
Neoarsphenamin doses, average	19	17	19	20	12	18
Mercury doses, average	7	5	9	6	8
Wassermann negative after above . . .	6	18	1	..	1	..
After above, per cent negative	60	22.5	9	..	33	..
Remaining negative under bismuth, per cent	100	100	100	..	100	..
Cases positive at start of bismuth . . .	4	57	10	14	2	16
Negative after bismuth	4	32	4	3	..	9
Made negative by bismuth, per cent . .	100	51	40	20	..	56
Injections of bismuth to obtain negative Wassermann, average	10	13	16	17	..	17
Cases reverting to positive	5	2	2	..	1
Cases unaffected by all therapy	23	6	11	2	7

2. *Latent Syphilis.* The effect of this combined intensive therapy is but little less striking when used in the treatment of latent syphilis. Of 18 cases treated, 14 became serologically negative in an average of 7 doses. As to the persistence of the negative Wassermann reaction in these cases, I am unable to draw conclusions for the time has been too short. Six of the patients disappeared from the clinic after obtaining negative blood reports. Two of these were brought back after several months and were found to be again serologically positive. A third case reverted to a positive after a short rest. The remaining 7 negative cases have remained persistently negative to date under further treatment with bismuth alone. Comparing the effects of this intensive method of treatment with the results obtained by the use of alternate courses of neoarsphenamin and bismuth or neoarsphenamin and mercury, the first named is strikingly superior. It is of extreme importance that none of these cases developed albuminuria at any time in spite of the intensity of the treatment.

The rationale of giving one injection of an arsenobenzene and one injection of bismuth in the same week is obvious. In the arsenobenzenes we have direct spirocheticides, whose action though powerful is of short duration; in bismuth we have a drug, which though spirocheticidal to a less degree, probably has the effect of stimulating natural resistance on the part of the tissues and which being absorbed daily in small amounts continually bombards the infection.

There are no rest periods which permit the reestablishment of spirochetal foci. The use of mercury in the same way has been decried because of its greater tendency to damage the kidneys and thus interfere with the free elimination of arsenic.

Benignity of Bismuth. Aside from its powerful action in all stages of syphilis, bismuth deserves especial recognition because of its low toxicity. In three years the writer has never observed stomatitis of a sufficient degree to warrant discontinuation of the drug, and this is the more remarkable in view of the fact that the majority of the patients treated in this clinic are of a class that pay but scant attention to buccal hygiene. It is customary for a blue line of greater or lesser intensity to develop on the gum margin after a total of from 300 to 500 mg. of potassium bismuth tartrate intramuscularly, but this offers no contraindication to its continuance. Foul breath is also common.

Just how many of the 40 or 50 odd cases that discontinued treatment did so because of local pain produced, it is difficult to say. In 7 instances, patients reported to the writer that they were unable to continue injections because of the local pain. Many patients reported that they preferred the intramuscular injections to intravenous injections.

Occasionally nodes would develop, but these quickly disappeared under local massage and hot applications. One of the most frequent symptoms complained of was that of muscular weakness developing a day after the injection and persisting for several days. The cause of this is unknown.

Eczematoid eruptions developing during the course of bismuth therapy were observed in 5 cases, and close study of these cases suggested very strongly that the eruptions were actually due to the bismuth.

Albuminuria was exceedingly uncommon, occurring in only 4 cases and then only faint traces of albumin being observed in the urine. A number of patients showing more or less marked albuminuria while receiving neoarsphenamin remained free of albumin while receiving bismuth.

The rarity of untoward symptoms may be partially explained by the fact that the author used smaller doses of bismuth than are employed in France where bismuth was first used in the treatment of syphilis.

Comment. The results obtained in these cases would indicate that bismuth deserves a high ranking among antisypilitic remedies because of its ability to favorably influence the Wassermann reaction and because of its low toxicity. Other writers, and many of them, have shown the specificity of bismuth *per se* in the presence of active syphilis of all types.

Oftentimes the Wassermann reaction will become negative some weeks or months after the cessation of all antisypilitic therapy

and it is possible that a certain per centage of the cases in this series which were still positive after receiving a considerable amount of neoarsphenamin would have become serologically negative had the bismuth not been used. However the majority of these patients had been under observation for a considerable length of time and had had rest periods without this occurring.

The majority of patients under treatment in our syphilis clinic at the present date are cases in which it is not desirous to employ the organic arsenicals, and indeed it would appear that the organic arsenicals are woefully lacking in ability to reduce the positive Wassermann reactions to negatives except in very early cases of syphilis. The value of bismuth is becoming more and more evident. Given in early syphilis its spirocheticidal activity is but little less than that of the arsenobenzenes and yet it does not provoke the severe reactions that are not uncommon following the initial dose of an arsenobenzene. Therefore it is an excellent drug to give at the start of the treatment of primary and secondary syphilis. Because of its action in reducing positive Wassermann reactions to negatives in a large percentage of cases of syphilis it is an excellent drug to be administered in cases of latent syphilis or so-called Wassermann-fast syphilis. Because of its low toxicity and painlessness as compared with mercurial salts administered in the same way, it is the drug of choice as a synergist to the arsenobenzenes.

Summary. In this study of the action of bismuth as a synergist to neoarsphenamin in all stages of syphilis, 160 cases are reported. In 128 of these cases the bismuth was given after the patient had already received one or several courses of neoarsphenamin and in some instances a few injections of mercury. Only 26 cases out of these 128 (or approximately 20 per cent) were Wassermann negative after an average of 18 injections of neoarsphenamin and 6 injections of mercury salicylate. Of the 102 cases still Wassermann positive, 52 (or 51 per cent) were serologically negative after an average of 15 injections of 100 mg. each of bismuth, given intramuscularly. Of this number, 5 cases of latent syphilis, 4 cases of tertiary syphilis and 1 case of congenital syphilis reverted again to a positive at a later date.

One of the most important facts disclosed by this study is that, of the cases which were serologically negative after treatment with neoarsphenamin and mercury, every one remained persistently negative upon the continuation of the treatment with intramuscular injections of bismuth. With this knowledge one may feel reasonably safe, once having obtained a negative Wassermann reaction in early syphilis, in continuing the treatment with intramuscular injections of bismuth in small doses, thus avoiding the dangers of too much arsenical therapy.

Administering each week one injection of bismuth intramuscularly and one injection of neoarsphenamin intravenously proved highly

successful in the treatment of early syphilis and latent syphilis. In secondary syphilis the cutaneous manifestations disappeared with astonishing rapidity and the blood Wassermann reactions were reduced from strong positives to negatives in an average of six weeks. This negative result has been persistent to date in all cases. In latent syphilis, 14 to 18 cases treated became negative in an average of seven weeks, but four of these were again positive at a later date.

SEROLOGIC STUDIES OF PROTEINURIAS.

RESULTS OF PRECIPITIN TESTS FOR SPECIFIC HUMAN BLOOD PROTEIN IN 100 CASES AT THE SALT LAKE COUNTY GENERAL HOSPITAL.*

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IN spite of the fact that serum albumin is the most common protein in the urine in pathologic states, we quite commonly find other proteins such as serum globulin, hemoglobin, albumose, fibrin, peptones and a large series of foreign proteins. The etiology of these proteins may result from the destruction or filtration of body proteins or the filtration of induced proteins. It may be of vast significance in some cases to determine whether the protein found in the urine is derived from the blood stream or whether it originates elsewhere.

Many writers have attempted to account for the abnormal presence of urinary proteins. Granger Stewart¹ showed that albumin in the urine may be accounted for by epithelium and other débris. Ott² has shown that nucleoprotein may be present in healthy urines. Almost every method of protein identification has been applied to some extent in the past. Cramer,³ in 1908, noted that the injection of egg white and ox serum into the dog produced coagulable protein in the urine. Condorelli⁴ has shown that proteins may be isolated from the urine which are not coagulable by heat or acetic acid.

The proteins in the urine which give a positive chemical test for albumin have not been completely classified serologically, and those proteins which fail to give a chemical test in the urine have been ignored.

A great amount of work has been done on the chemical and serologic detection of proteins introduced both enterally and parenterally.

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Hamburger,⁵ Michaelis and Oppenheimer,⁶ Friedenwald and Isaac⁷ and others have been identified with the serologic protein tests for many years. They, however, limited the greater part of their work to protein detection in the blood of the human or animal tested. Furthermore, like the majority of authors, they have spent most of their time isolating foreign proteins. Very little work appears on the detection of specific hemic proteins in the urine serologically. The writer has been particularly interested in the specific detection of protein in the urine.⁸

The close observation of mild and transient proteinurias occurring so frequently in cases entering a general hospital made a specific precipitin study of these urines seem worth while. This brief study of 100 cases is an attempt to determine the presence of hemic proteins in the urine of patients coming under my observation at the Salt Lake County General Hospital. The writer chose the detection of blood proteins in the urine for the following reasons: (1) The frequency with which leukocytes and red blood cells are found in the urine. (2) Infection is almost always accompanied by a fight between the bacteria and the blood cells, with the resultant disintegration of some of the blood. Dochez and Avery were able to detect precipitin in the urine of patients suffering with pneumonia.⁹ (3) Destruction of blood cells is a constant physiologic process in healthy individuals. (4) Blood protein cannot at all times be utilized by human organisms, especially after injury, operative procedure or hemorrhage.

A hundred cases of varied diagnoses were chosen at random. Forty per cent of these gave a positive chemical urinary protein test. The majority of these positive tests, however, presented protein in amounts varying qualitatively from a very faint trace to a definite trace. Some of these proteinurias were classed as nephritic while other were ignored so far as clinical observation was concerned. Whether ignored or used as an aid in diagnosis, we cannot consider the results obtained by chemical urinary protein tests accurate for diagnostic purposes in all cases, for they fail to take into consideration the following states in which protein may be found in the urine: (1) Postoperative proteinuria; (2) postpuerperal proteinuria; (3) alimentary proteinuria; (4) orthostatic proteinuria; (5) postfebrile proteinuria.

In these types of proteinurias where definite evidence of nephritis is lacking, a specific test to determine the etiology of the protein seems indicated.

The technique of the precipitin test was as follows: A healthy rabbit was inoculated daily with increasing doses of fresh human whole blood until its serum titer became high (1 to 60,000). The rabbit was then bled by cardiac puncture. The serum was separated and used immediately in the precipitin tests. To 3 cc. of filtered urine 0.2 cc. to 0.5 cc. of the antihuman rabbit serum was added at room temperature. Readings were taken within one hour of

TABULATION OF BLOOD—URINE PRECIPITIN REACTIONS.

Diagnosis.	No. cases.	Control urine.	0	$\frac{+}{=}$	\pm	+	++	+++	Nitric acid test.	Acetic acid test.	Negative (%).	Positive (%).	
Pulmonary tuberculosis	24	Clear except tuberc. kidney	14	5	0	3	0	2	$\frac{+}{7}$ 0 17	$\frac{+}{9}$ 0 15	60	40	
Scarlet fever	1	Clear	0	1	0	0	0	0	1	0	1	0	100
Acute endocarditis	1	Clear	0	0	1	0	0	0	1	0	1	0	100
Pregnancy	8	Clear	2	1	0	2	3	0	6	2	6	2	73
Acute nephritis	1	Slight cloudiness	0	0	0	0	1	0	1	0	1	0	100
Diphtheria	4	Clear	2	0	1	0	1	0	2	2	2	2	50
Chronic arthritis	2	Clear	0	0	0	1	1	0	1	1	1	1	100
Bronchitis	2	Clear	1	1	0	0	0	0	0	2	0	2	50
Typhoid fever	2	Clear	1	1	0	0	0	0	1	1	1	1	50
Inoperable gastric carcinoma	1	Clear	1	0	0	0	0	0	1	0	1	0	100
Bronchial asthma	1	Clear	1	0	0	0	0	0	0	1	0	1	100
Tabes dorsalis	2	Clear	0	1	1	0	0	0	2	0	2	0	100
Cerebral hemorrhage	2	Clear	1	0	0	1	0	0	1	1	1	1	50
Attempted suicide	1	Clear	1	0	0	0	0	0	0	1	0	1	100
Neuritis	1	Clear	1	0	0	0	0	0	0	1	0	1	100
Diagnosis unknown	1	Clear	1	0	0	0	0	0	0	1	0	1	100
Chronic endocarditis	6	Clear	4	1	0	1	0	0	2	0	3	0	80
Septicemia	1	Clear	0	0	0	1	0	0	1	0	1	0	100
Cystitis	1	Clear	0	0	0	1	0	0	1	0	1	0	100
Diabetes mellitus	1	Clear	1	0	0	0	0	0	0	1	0	1	100
Broncho-pneumo. . . .	1	Clear	1	0	0	0	0	0	0	1	0	1	100
Duodenal ulcer	1	Clear	1	0	0	0	0	0	0	1	1	0	100
*Acute cholecystitis	2	Clear	0	0	1	1	0	0	2	0	2	0	100
Bartholin abscess	1	Clear	0	0	0	1	0	0	1	0	1	0	100
Acute fractures	4	Clear	4	0	0	0	0	0	0	1	0	1	100
Adenoma thyroid	1	Clear	0	1	0	0	0	0	1	0	1	0	100
Paranephric abscess	1	Clear	1	0	0	0	0	0	0	1	1	0	100
Kidney sarcoma	1	Clear	0	0	1	0	0	0	1	0	1	0	100
Infected leg	1	Clear	1	0	0	0	0	0	0	1	0	1	100
Empyema	2	Clear	1	0	1	0	0	0	0	1	0	1	50
Carcinoma, uterus	1	Clear	0	0	0	0	1	0	1	0	1	0	100
Osteomyelitis	2	Clear	0	0	0	2	0	0	0	1	0	1	100
Inguinal hernia	2	Clear	0	1	0	1	0	0	1	1	1	1	100
Varicose ulcers	1	Clear	0	0	0	1	0	0	1	0	1	0	100
Cholelithiasis	3	Clear	1	0	0	1	1	0	2	1	2	1	33
Bullet wound	1	Clear	0	0	1	0	0	0	1	0	1	0	100
Ischiorectal abscess	1	Clear	0	0	1	0	0	0	1	0	1	0	100
Appendicitis	11	Clear	7	2	0	2	0	0	3	8	3	8	84

Total number of cases 100
 Number of negative cases 48
 Number of positive cases 52

* This and the cases following are postoperative.

CODE TO PRECIPITIN REACTIONS: 0 = negative; $\frac{+}{=}$ = faint trace; \pm = trace;
 + = light cloud; ++ = cloud; +++ = heavy cloud.
 CODE TO CHEMICAL TESTS: + = positive; 0 = negative.

mixing the serum. A nitric acid protein test and an acetic acid protein test were done on each urine tested. The results of the precipitin test on the one hundred different urines is recorded on Chart I. A preservative was not added to the sensitized serum because of its tendency to cause slight cloudiness, thereby giving rise to possible source of error. Furthermore, all the urine specimens were collected at the time the sensitive rabbit serum was freshly prepared.

Fifty-two of the 100 urines examined gave a positive precipitin test. The chemical protein tests were positive in 40 cases. The results obtained by the chemical tests varied from the results of the precipitin tests.

Fifty-seven per cent of the surgical cases in this series presented a positive precipitin test. The large majority of these cases were postoperative. Of the medical cases in this series 49 per cent were positive. All precipitin tests were compared with clear urinary controls.

Conclusions. The following preliminary conclusions can be drawn from this study: 1. Blood protein was detected in 52 per cent of the cases studied. This blood protein can be specifically identified in the urines of the cases tested by the precipitin test.

2. The detection of specific blood protein in the urine by the precipitin test does not parallel the positive chemical protein tests.

3. The presence of blood protein in the urine is not characteristic of any particular disease or type of case.

4. The most marked reactions found in this series were in cases of tuberculosis of the kidney, pyelitis, pregnancy and cancer of the uterus.

5. We can account for at least some of the proteinurias with or without renal pathology, by the presence of blood protein in the urine.

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THE DIAGNOSIS OF TRACHEOBRONCHIAL TUBERCULOSIS.

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THE literature of tracheobronchial and "hilum" tuberculosis is voluminous. The major part of it deals with physical signs and symptoms assumed to be associated with this condition. The descriptions of the actual lesion as demonstrated by Roentgen ray are somewhat vague both as to site and appearance. Not a few observers report calcification due to tuberculosis in the majority of all patients, whether or not they have been exposed to an open lesion. Many are governed in their recognition of the pathologic and anatomic lesion by the presence of a tuberculin reaction, and the association of evidence such as underweight, fever, cough, night sweats, fatigue and dyspnea, which are generally assumed to be allied with and to result from the lesion. It is desirable to consider the possibility of consistent and reproducible demonstration of tracheobronchial tuberculosis. If we are to understand its pathogenesis and symptomatology, those cases showing roentgenographically reproducible lesions must be studied apart from the group whose anatomic diagnosis has rested on various symptoms. As has been shown elsewhere¹ these lesions are frequently the forerunners of diffuse pulmonary infiltrations. While there is no evidence that it is the source of these infiltrations, and much that it is not,² tuberculous tracheobronchial disease is an indication of severe infection, and such infection may not only be carried to the lymph nodes but may also remain latent in the lung and develop after the glandular disease gives evidence of healing.

The matter of roentgenographing the lungs and of determining what abnormal changes could be conclusively recognized has occupied the writer for some seven years. The subject was approached in two main studies, one to discover what elements of the lung structure might be differentiated roentgenographically under the simplest conditions, the other to provide against the effect of cardiovascular movement in disturbing lung detail. The mechanism, methods and some conclusions of the latter study³ have already been briefly reported.

The former aim was sought by roentgenographing the excised lung, and then comparing the specimen, area by area, with the roentgenogram. Some 400 pairs of lungs were thus examined, about 150 of these being maintained inflated during exposure. Excised lungs have the advantage of relative availability and ease of handling; and slightly finer detail may be shown when the ray can

be decreased to what is just sufficient to penetrate the lung itself. Furthermore, no contiguous structures, such as spine, mediastinum and sternum, complicate the shadow, a matter of importance in discovering the roentgenographic demonstrability of normal and pathologic lymph nodes of the tracheobronchial and intrapulmonary groups. In this paper the lymph nodes lying within the lung will be described as intrapulmonary, those outside as tracheobronchial. The division is artificial pathologically but convenient for anatomic and roentgenologic descriptions.

In passing it may be noted that in this series of pathologic specimens, which was examined by Dr. Opie, the pulmonary primary lesion was demonstrated in the lung substance in all but about 1 per cent of the cases in which a glandular lesion was observed. It was at least as frequent that a pulmonary primary nodule occurred without a glandular lesion as that the reverse was found. Below are given the anatomic and roentgenographic characteristics by which particularly the lymphatic element of the associated primary pulmonary and glandular lesions⁴ may be conclusively recognized. But the criteria apply equally to those pulmonary primary lesions which are situated in the parenchyma close to the main stems, for example on the medial aspect of the lung, subpleurally at the inner part of the interlobar fissures, or, more rarely, in the lung substance which lies about the main stems. Frequently the pulmonary primary lesion is larger than the glandular (Fig. 9), and constitutes a greater menace; frequently it progresses into a diffuse or localized infiltration, usually nonapical because the originating primary foci, distributed in proportion to lung volume, occur more commonly in the lower part of the pulmonary cone. But from the diagnostic point of view, the pulmonary primary offers few difficulties in recognition because it is usually situated subpleurally⁴ and therefore occurs chiefly at the periphery (Fig. 9). It is, in consequence, rarely to be confused with or obscured by trunk shadows, and is obvious, unless it lies behind the cardiac or diaphragmatic shadow. Here too it may be demonstrated, if calcium-bearing, by the proper quantity of Roentgen ray. And even when calcium-free, if it lies clear of other densities, the pulmonary lesion can be recorded at least as well as the vascular branches of supply in the area in which it is situated. Excised lung studies show the calcium-free pulmonary primary to be as dense, per unit of volume, as artery or vein and consequently, when synchronization permits the recording of fine vascular detail, any equally fine pathologic detail will be shown at least as well. Subpleural densities are remote from the effect of cardiovascular vibration, described later, and if anterior, are especially favorably situated for accurate representation.

The term tracheobronchial tuberculosis is preferable to hilum tuberculosis because, as pointed out by Opie, the former describes accurately the glandular element of the complex of primary infection.

The lesion rarely breaks through the gland capsule, and if it does the rupture is usually into a bronchus, artery or vein. Direct progression through the capsule into the areolar tissue of the hilum was seen only once in a series comprising over 400 specimens, including many fatal infantile cases. While infiltrations occur involving the parenchyma near the main bronchial and vascular stems, in our studies, both of postmortem material and of living persons, it could be shown by careful examination that there was also an apical lesion, and the presumption is that, for the most part, localization near the root is merely one of the less common manifestations of bronchogenic extension. Furthermore, it was notable in the excised lung series that frequently, in the presence of a slight apical lesion, a more definite infiltration in the upper part of the lower lobe or the anterior lappet of the upper lobe gave the roentgenographic appearance sometimes described as hilum tuberculosis. Even in good stereoscopic films in the living it is not always possible to define the plane in which a lesion lies. Section will decide the question in the excised, and variations in the patient's position will solve it in the living.

The postmortem material for this study comprised many lungs free from gross lesions or even agonal edema. From these a good conception was obtained of the number of trunks that might be recorded. They are strikingly more prominent (Fig. 1⁵) and numerous than in the films of normal persons in life, and more bronchial bifurcations, the site of nodes, are rendered visible. On section of the lungs special attention was directed to the possibilities of roentgenographic localization of the lymph nodes, both the normal and those showing various stages of fibrous and inflammatory change. Meticulous study of the films was made in cases showing diverse types of nodes, from the dense, fibrous, coal-pigmented lymph node of the city dweller, and the succulent nodes of acute, nontuberculous bronchopneumonia, through the stages of fresh semifluid and old putty-like caseation, to the stony nodules and masses of dense calcification. In summary, it was found, as regards the nodes of the trachea and extrapulmonary bronchi, that only when calcium infiltration of a necrosed area was present was there any distinctive shadow. As regards lymph nodes within the lungs, it was found that the presence of calcium was the only roentgenologic indication of the presence and site of a lymph node, except for that segment of the noncalcified margin of such large calcium-bearing glands as projected laterally to the main stems and larger branchings of the air and blood-bearing trees and so contrasted with pulmonary parenchyma. Intrapulmonary nontuberculous glandular enlargement sufficient so to project was not seen, although there were many specimens showing large, succulent glands due to acute infections. Such glands did not throw shadows to be differentiated in the composite shadows of the main stems and their branches

which cross and surround the glands, and this study affords us no reason to suppose that they may be recorded in the living, or confused with tuberculous disease. While this finding is contrary to the inferences to be drawn from many articles, it is in harmony with the properties of the Roentgen ray, which is obstructed, per unit of volume, only in relation to atomic weights. Furthermore, although many roentgenograms were made during and immediately after acute, often serious, infections in children at all ages, in no case was there evidence of roentgenographic demonstrability of glands of the tracheobronchial group referable to the acute infection, that is, calcium-free.

Reference to Figs. 1 and 2 (see also Fig. 1⁵) will show how well adapted to the fullest representation of any normal or abnormal density was the material studied and the method of making the stereoroentgenograms. The trachea and bronchi with their sheathing tissues stand out clearly. Except for the surrounding areolar tissue and occasional tags of the great vessels, all that might obscure the lymph nodes was removed. The lungs were inflated until the air entered everywhere, then allowed slightly to subside so that the pleura should not be unnaturally tense. The total volume of air contained, and consequently the basis for securing contrast was similar to that existing *intra vitam*. The lungs were allowed to hang freely, and it was sought to keep them in a position as nearly normal as possible merely by their apposition to the front of the cassette changer. Occasionally string or gauze was used to separate the bases. Stereoscopic exposures were made, the duration varying from one-fiftieth second to one-twentieth second; rarely as much as one-tenth second was used. The photographic effect sought was that giving the greatest detail. The relation of the quantity of exposure to that of the living was about 60 to 75 per cent. The absence of the chest wall reduced the amount necessary. It was found that full exposure, as for the living, marred the detail in the periphery but that otherwise the films were similar.

Clearly, tracheobronchial lymph nodes, both those lying immediately outside the lung and those further cephalad on the bronchi and trachea, are favorably situated, in the excised lung, for the fullest demonstration of changes in contour and density. Yet in all the specimens studied partial outlines of only two lymph nodes could be made out lying within the shadow cast by the ensheathing areolar tissue. In all other cases, apart from calcium infiltration, when the site of nodes could be determined from the film, it was due to enlargement; whether the cause of the enlargement was coal-pigmented fibrous tissue or acute edematous swelling, its indication of the site was due to the size, not to the intrinsic density of the node. That is, only in instances where the node projected laterally from the trachea or bronchi, bulging out the sheath of areolar tissue, was its contour indicated. Otherwise, even if a

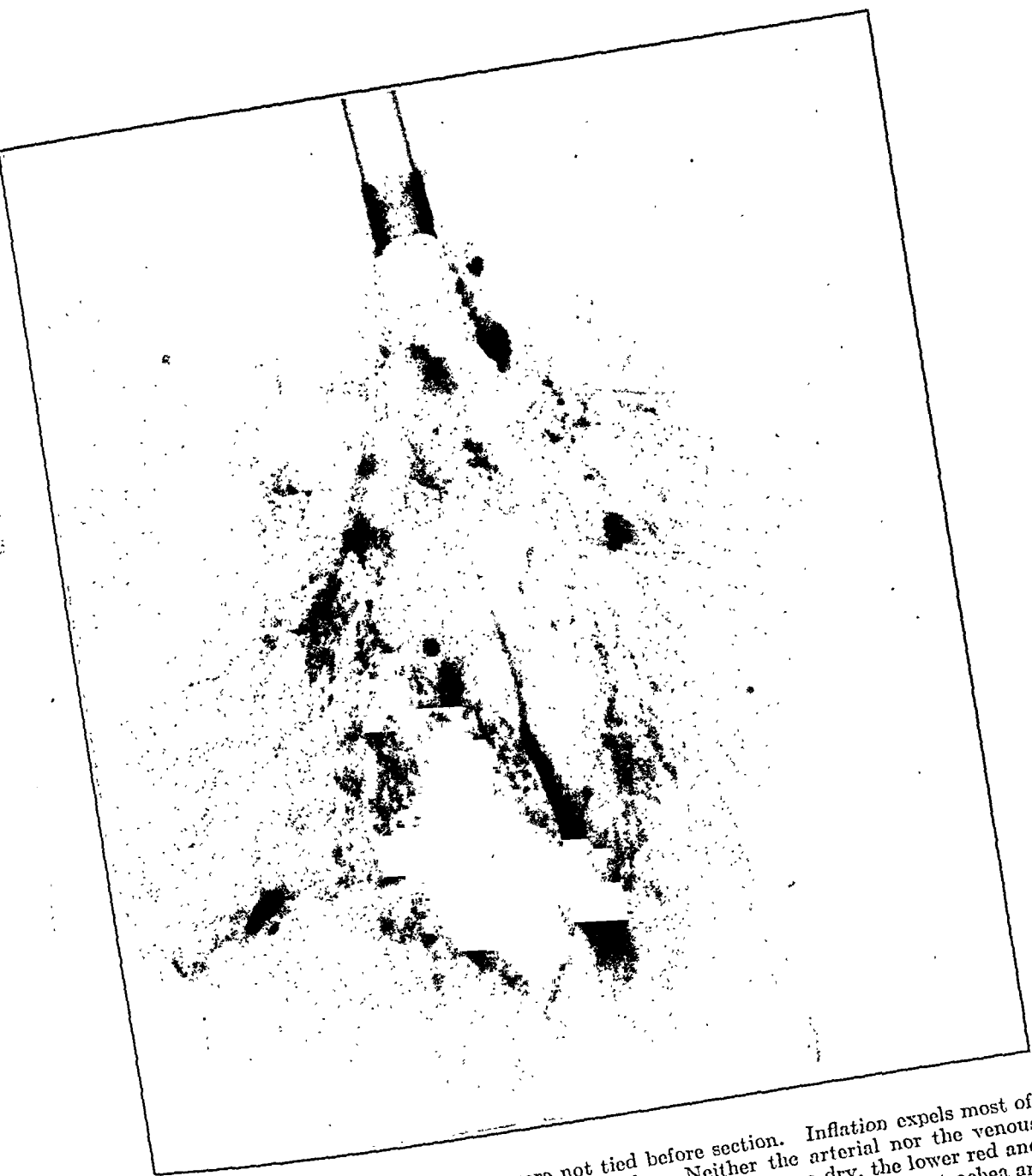


FIG. 1.—Right lung: The vessels were not tied before section. Inflation expels most of the unclotted blood and these lungs contain little. Neither the arterial nor the venous main stem can be seen. On section, the upper and middle lobes are dry, the lower red and contains fairly abundant fluid. At the hilum, the carina and to the right of the trachea are hard, anthracotic, fibrous lymph nodes containing hard calcified masses. Left lung: The left lung resembles the right. There is a firmly calcified nodule in the upper lobe. The nodes at the hilum resemble those on the right. There is no evidence of the presence of the uncalcified part of nodes except for the calcium-containing bulge above the left bronchus. The fibrous, pigmented glandular margin is no denser than the ensheathing areolar tissue.



FIG. 2.—The vessels were not tied before removal of the lungs. There is a dense calcium shadow at the carina, two others lateral to the right main stem bronchus and one in the substance of the right lung. The glands containing the calcium at the carina and on the bronchus are not distinguishable, although the one at the carina is particularly favorably situated. The fibrous capsule enclosing the mass in the lung substance throws a faint halo-like shadow.

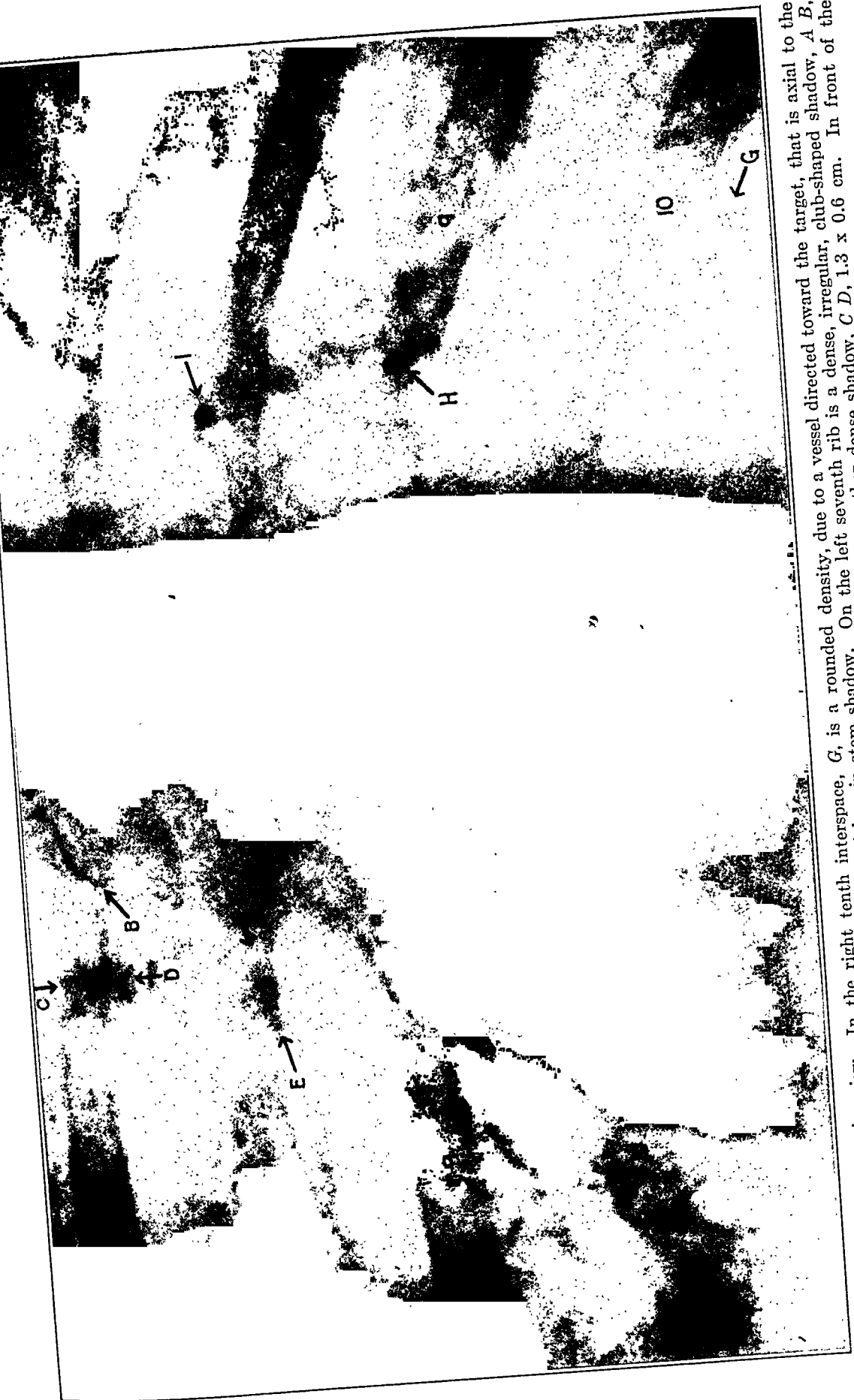


Fig. 4.—A postero-anterior view. In the right tenth interspace, *G*, is a rounded density, due to a vessel directed toward the target, that is axial to the incident ray. Similar densities, *H* and *I*, appear on the arterial main stem shadow. On the left seventh rib is a dense, irregular, club-shaped shadow, *A B*, 1.7 x 0.7 cm., its head touching the aortic contour. One centimeter lateral to its lower end is another dense shadow, *C D*, 1.3 x 0.6 cm. In front of the eighth rib, on the arterial main stem shadow, is a granular density, *E F*, 1.7 x 0.8 cm..

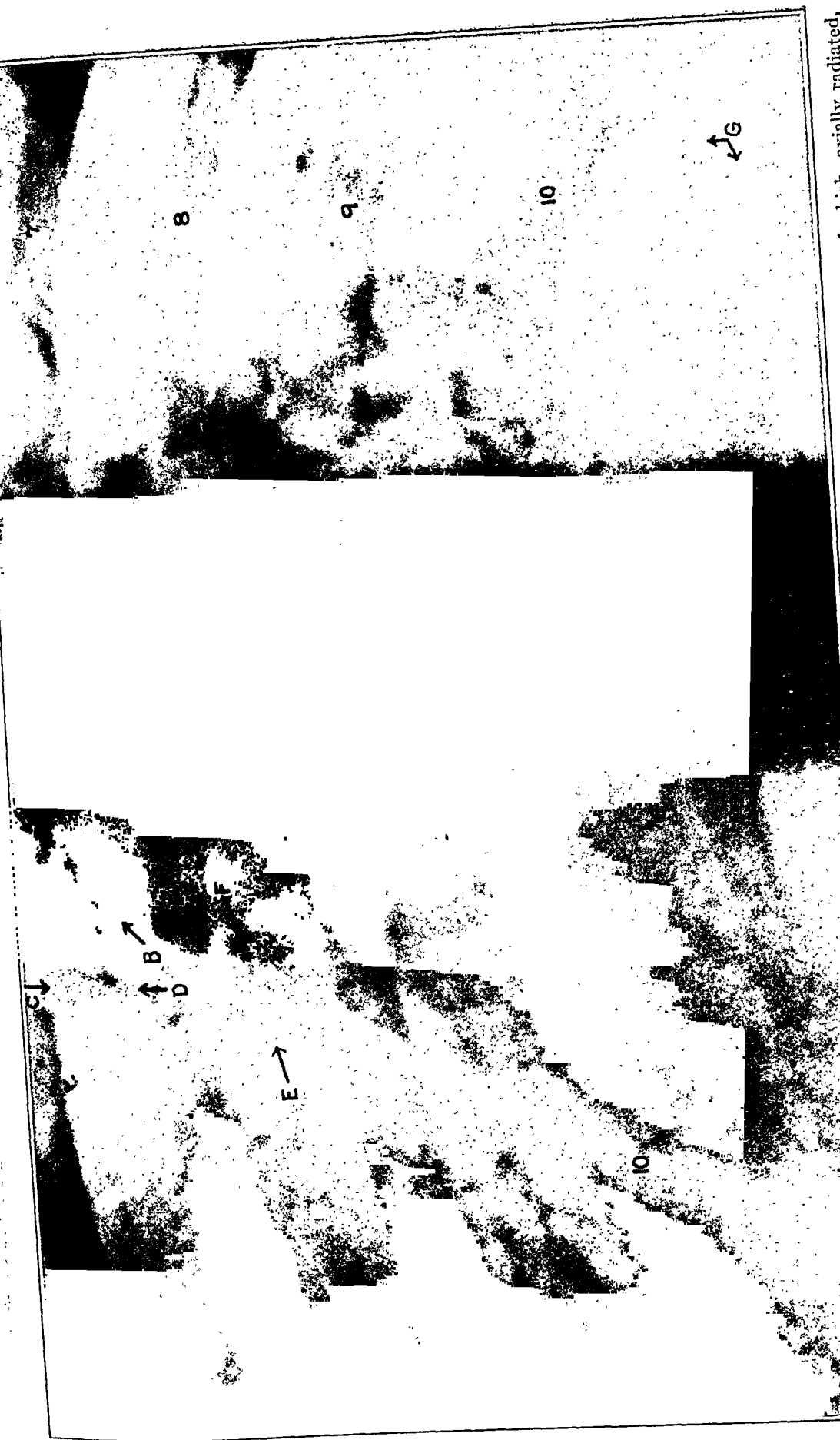


FIG. 6.—A rotation exposure. The rounded spot *G*, in the right tenth interspace is replaced by a Y-shape vessel, the upper arm of which, axially radiated, caused the density *G*. The lesions on the left can be recognized as persisting. *C* *D* is more clearly defined, seen from the new angle; *E* *F* in the eighth interspace is now partly behind or upon the cardiac shadow.

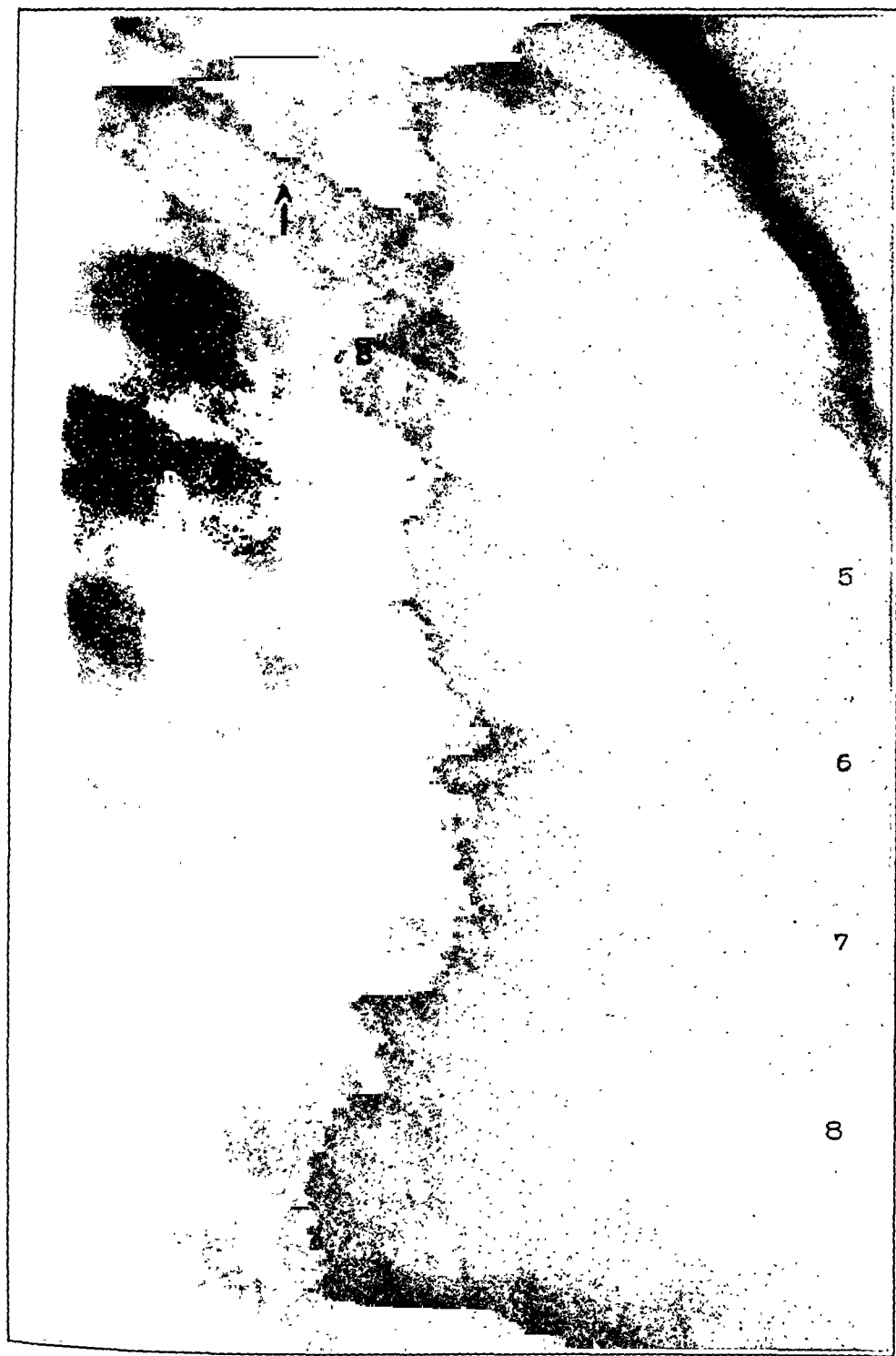


FIG. 8.—Left anterior oblique exposure of a boy, aged seven and a half years, in contact with a tuberculous father (sputum positive) during four and a half years until one and a half years prior to this roentgenogram. Close to the right side of the trachea, above the carina, at the level of the fifth rib and interspace and the sixth rib are two oval outlines. The lower pole of the upper one, the long axis of which is indicated by A, overlaps the upper pole of the lower one, the long axis of which is indicated by C. Their lateral borders cross at B. The lower one is not unlike the nucleus of an epithelial cell, with a dark, oval outline and an irregular dark spot within it, at the sixth interspace level. D, E, F, mark the upper pole, posteromedial border, and lower pole of another oval density lying posteromedial to the right bronchus below the carina, which is crossed by the sixth rib. These densities are due to scant calcium infiltration of caseous glandular necrosis. Neither of these shadows could be seen in the postero-anterior position. The outlines of the glands enclosing the calcium-bearing necrosis can be seen neither in the illustration nor in the film from which it was taken. There was no mediastinal bulge. The left bronchus passes in front of the spine at the level of the seventh rib. The lower end of the right bronchial main stem is marked by G. The patient was well nourished and active, pulse and temperature were normal. There were no complaints nor symptoms.

node contained calcifications or caseation impregnated with calcium, the shadow recorded conformed only to the outlines of the calcium-bearing lesion. The peripheral lymph tissue, whether hypertrophic or fibrous, and the gland capsule were not dense enough to cast a shadow differentiating them from the contiguous areolar tissue. Glands containing soft fresh caseation due to acute, rapidly advancing infections were similar in density to nonspecific edematous nodes. They were distinguishable only if large enough to bulge out the silhouetté of the areolar mantle (Fig. 1.)

In discussing the recognition of intrapulmonary lesions, it is necessary to consider at each point what modifications of the appearances seen in roentgenograms of the excised lung are effected by cardiovascular movement in films of the living. The intrapulmonary nodes and lymphoid masses, situated at the forks of branchings of the bronchial tree, are surrounded by structures of roentgenographically equal density. In proportion as one approaches the hilum and the nodes are larger, they are crossed, surrounded and overlaid by arteries, veins and other bronchi converging on the main stems. The vascular trunks, at least, are, per unit of volume, as dense to the Roentgen ray as are normal nodes, or, indeed, any nodes, without calcium infiltration, as pointed out above. The glands most frequently and severely infected, those which lie just lateral to the main stem bronchus (Figs. 1, 2 and 4), that is, on the side whence the bronchial trunks arise, are not only crossed by the venous trunks but have superimposed on them the main arterial stem. In order for nodes so situated to be recognizable roentgenologically they must, unless containing calcium, project not only beyond the shadow of the main arterial stem but also beyond the zone where the crossing of the converging vascular trunks forms a complex, unequal shadow, for only so can they be shown in contrast to the air-bearing parenchyma. In the living this zone is particularly confusing when the exposure is as long as the cardiac cycle, because of the effects of cardiovascular movement; or, when a shorter time is used, if the exposure chances to occur during systolic movement. Diastolic rapid exposures (not more than 0.05 second at pulse rates about 100), are best adapted to show the origin, course and branchings of trunks, and to differentiate abnormal glandular enlargements which may project into this zone.

We have seen, in our excised lung series, no instance of a noncalcium-bearing gland projecting beyond the arterial main stem shadow, and only one instance in the living. In this case repeated, but not yet protracted, observations, suggest a tuberculous etiology. Not infrequently a calcium-bearing gland is seen to project, and to show, laterally, a margin surrounding the calcium-bearing necrosis, its peripheral contour standing out against the less dense pulmonary parenchyma into which it bulges. It is somewhat more common to find such a gland to lie wholly medial to the lateral margin of the

arterial main stem. Then only the calcified area is visible (Figs. 4, 5 and 6), the remainder of the gland being no denser than the arterial main stem shadow and the maze of vascular trunks abutting on it and crossing it in many directions.

A common source of diagnostic error is the sharp, round shadow cast by a vascular trunk directed toward the target so that the incident or primary ray is approximately axial (Figs. 3, 4, 5 and 6); or the semioval shadow often recorded when the plane of the curve of a vascular trunk is directed slightly above or below the axis of the ray. Each of these is comparable to and often situated beside the dense ring-shadow due to a bronchus directed toward the target. The former is more common and may occur anywhere in

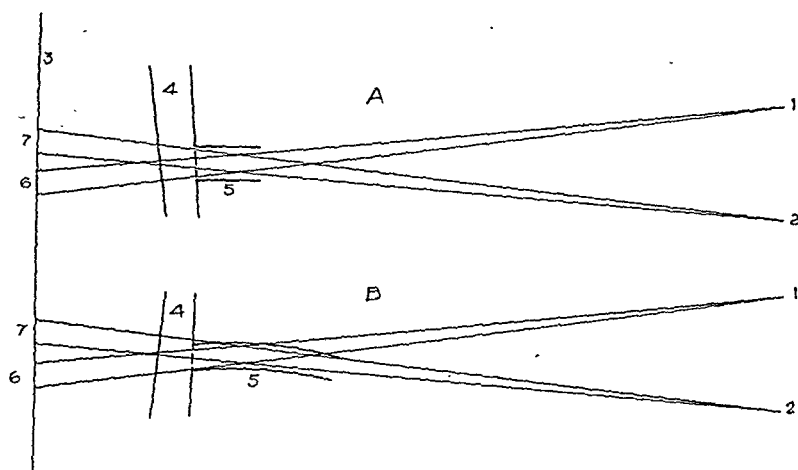


FIG. 3.—The stereoscopic drop is exaggerated to facilitate drawing. Actually the two rays intersect at a more acute angle and may consequently be practically axial to narrower vessels. 1, Ray from upper position of tube; 2, ray from lower position of tube; 3, stereoscopic films, represented as one; 4, vessel directed in plane perpendicular to axial rays; 5, axial branch; 6, shadow cast on film 1; 7, shadow cast on film 2.

the lung field except at the apex and the extreme lateral margin, inasmuch as branching of trunks continues well out to the periphery. In proportion as caliber diminishes these shadows of vascular causation are smaller peripherally. Those trunk shadows radiating from the hilum in planes nearly perpendicular to the incident ray often show the branches which arise from them axial to the ray as more or less well-defined dots particularly in the middle and outer third of the lung field (Fig 1⁵). Many of these dots are ill-defined and blurred when exposures occur during systolic movement and have been interpreted as thickening of the trunk on which they appear. The apical branches of supply, however, running straight into a rapidly narrowing cone, are little disturbed by vascular movement and frequently show these dotted vessels.⁶ Thus

branches arising parallel to the axial ray are responsible for many "beaded" trunks and practically always for the so-called "capped" trunks, which have been interpreted as due to calcium in a lymphoid mass at the bronchial bifurcation. In films of the excised lung, when the vessels are tied off before removal, the number of these round and oval shadows along the course of the vascular trees is amazing, and their nature may be verified by section. Practically, both for the excised and the living, the diagnosis may be made conclusive by appropriate methods. The proof lies in roentgenographing the beaded trunk from a slightly different angle, when it is seen that the dots have disappeared and that branches arise from their site. On the other hand, a calcified lymph node or pulmonary nodule may show a variation in contour but will not be lost by this procedure (Figs. 4, 5 and 6). For many such determinations the distance of the stereoscopic shift supplies the necessary new angle of radiation, when the films are truly stereoscopic, that is, when the lungs are undisturbed by changes in relative cardiac volumes and by differences in pressure in the elastic vascular tree.⁶ In other instances the conclusive differentiation of vascular artefacts from calcium-bearing lesions by stereoscopic exposure alone is not possible. It is apparent that even with a full stereoscopic drop and rapid diastolic exposures, the incident ray from both the target levels will be practically axial to the shorter, thicker trunks that run parallel to it (Fig. 3), or even to those narrower trunks whose natural curve forms an arc to the axial rays, so that at both stereoscopic levels a dense column of blood is opposed to the ray. The former condition frequently obtains upon and close to the arterial main stem, and medial to the main stem bronchus, due, respectively, to arterial and venous axially directed branches. Such vascular artefacts are especially disturbing in films of infants, and troublesome in those of older children. In infants the trunks closest to the main stem cause the artefacts, and these are large enough in proportion to the chest to suggest serious lesions. The older children show more numerous artefacts, since there are more vessels large enough to throw a shadow. Often in children of ten to fifteen years the very number and the uniformity of size, quality and distribution of these shadows is enough to cast doubt on their having a pathologic significance.

The type of vascular artefacts due to a curving vessel axial to the incident ray is seen commonly at the posterior level of the fifth and sixth interspace, right and left.

It was found that exposures made at various points above and below the usual stereoscopic upper and lower levels commonly failed to solve the nature of those questionable shadows. This is due to the large number of branches arising at every level from the main vascular stems. Thus one could not be sure, even after a shift, of, say, 7 inches below the usual stereoscopic midpoint, if a

persisting density were not simply a new vessel coming off lower down. It was then found that a slight rotation of the patient about his perpendicular axis was of great value in deciding the question. After many trials, I have sought to rotate the patient so that the right cardiac border coincides in the film with the right border of the spine. A single exposure so made at the lower stereoscopic level has enabled us to determine the identity of practically all densities lateral to the spinal border, right and left (Figs. 4, 5 and 6). Only very occasionally is it desirable, chiefly for the diagnosis of densities lying near the bronchus to the left upper lobe, to rotate the patient in the opposite direction (that is, the right shoulder and hip away from the cassette changer, and to the same degree as for the above noted left-shoulder-off position).

The addition to the usual stereoscopic technique of the first described left rotation (left side away from the film) is of value not infrequently in the diagnosis of lesions sufficiently unstable to warrant careful oversight and reduced exertion to ensure their healing. Many intrapulmonary unencapsulated caseous necroses, containing only delicate and diffuse calcium infiltrations, can be certainly diagnosed by the addition of slightly rotated exposures. A true lesion will continue to be recorded in the rotation film as a shadow of constant quality, finely and irregularly granular, or made up of softly lamellated and crenated lines (Figs. 4, 5 and 6), or irregularly stippled; and its contour will show such slight changes as will be harmonious with that in the postero-anterior position. Artefacts, on the other hand, are resolved into their components or entirely disappear. Especially valuable is the rotated position in differentiating from true lesions the very common densities in the right cardiophrenic angle due to venous trunks, and the numerous spots in the inner third of the lung field due to arterial and venous branches. It is also often useful when it is of moment to diagnose densities in the outer half of the lung field. Naturally, as the caliber of the vessels diminishes peripherally, lesions likely to be confused with densities of vascular origin are smaller and of less clinical importance. Care must be taken not to turn this exposure into an oblique (see below), for in the oblique position a new and, for this purpose, confusing number of rounded densities occur, and it is difficult to determine which shadows one was seeking to resolve.

In many cases a position midway between the postero-anterior and the lateral is indispensable. In the roentgenographic recognition of tracheobronchial tuberculosis in the living, the shadows of spine and sternum offer a serious difficulty. Without the oblique exposure it is impossible to recognize clearly (see Figs. 7, 8 and 9) or even to suspect the presence of fresh and unstable tuberculous necrosis. Many calcium-bearing lesions, both at the carina and to the right of the trachea, measuring up to 2.5 cm. across, completely escaped demonstration in the postero-anterior position

(see Fig. 8, *D, E, F*). It is perhaps important here to emphasize what has been said above with reference to the excised lung, that calcium-free caseation, apart from mass and consequent projection into the lung field, is roentgenologically indistinguishable from the areolar tissue and vessels of the mediastinum. Caseation so extensive as to bulge into the lung field, a condition chiefly seen in infancy, must almost invariably prove fatal. In the living it is rare that a calcium-bearing tracheobronchial gland can be seen to project beyond the margin of the spinal shadow. We have not seen tuberculosis of the tracheobronchial glands cause a uniform, rounded mediastinal mass except in fatal infantile cases. A postero-anterior film showing smooth and oval mediastinal bulges should be scrutinized for distortion of the patient's position by which the shadow of the sternum appears to the right or left of the spinal shadow. Malignant tumors will rarely come in question in children. Rotation is probably responsible for the majority of apparent mediastinal enlargements. It is in infants and in children up to four years that most "broadened mediastinums" have been interpreted as pathological. Apart from errors due to rotation and to thymus shadow, exposures made during systole and during expiration are frequent causes of broadening of the mediastinum. After the fourth year response to the request for holding the breath is obtainable, and broadened mediastinum is rarer.

The chief value of the oblique position is that one is able to record the trachea, the carina and the two bronchi as far as their entrance into the lung in a way that is not possible when they are situated between the spine and sternum. Calcium-bearing necrosis throws its characteristic shadow, and while the gland in which it lies is not to be outlined, from the nature of the granulation, whether faint and small, or large, dense and confluent, one can estimate the condition and lability of the lesion. The longer calcium infiltration has endured, the better are the chances that the lesion has been walled off. We have, in three years observation, of cases reported elsewhere¹ found no evidence of reabsorption of calcium from glandular lesions. In several cases the shadow has become heavier and better delineated. Insofar as the glands are concerned, caseation if accompanied by calcium infiltration, appears to remain. In view of clinical and experimental evidence⁸ that reabsorption of caseous pulmonary and glandular infiltration occurs further and more extended observations on calcified glandular caseation are desirable.

The situation, extent and contour of the calcium-bearing glandular lesions have been of interest. As pointed out by Opie⁴, the common lesion in a lymph node above the carina (Figs. 1, 7 and 8) is almost always situated to the right of the trachea irrespective of the side in which the pulmonary and intrapulmonary glandular lesions occur. In the oblique view, it may be seen that the calcium-

bearing lesions lie close to the trachea and bronchi, and always, in our cases other than fatal infantile disease, leave a clear space between the posterior margin of the calcium-bearing mass and the spine.

The contour of the calcium shadow is various; rounded, oval, irregularly nodular, pear-shaped. But in all instances verifiable from two angles, a contour, however hazy, is perceptible. The contour may, of course, be referable to lesions in one gland or in more than one in apposition (Fig. 7, to right of trachea), in a plane lying parallel to or at various angles to the incident ray. Occasionally it is desirable to make oblique exposures at various angles to see the full extent of large lesions situated one behind the other in the line of the incident ray.

The oblique position used is one very similar to the left anterior oblique of Pritchard.⁸ A good view of the trachea and bronchi is obtained by using a position almost half way between the postero-anterior and the lateral. In the more nearly lateral positions there tends to be superposition of the two hilum shadows and the carina is not seen. In the oblique position the shadow of the aorta lies behind that of the spine. The trachea, carina and the full extent of the extrapulmonary bronchi are well seen. The patient stands with the head slightly inclined, the left arm hanging behind the left hip, the left antero-lateral chest wall against the cassette changer, the right forearm bent over the head, the elbow as high as possible. The scapula thus interferes not at all with the view of the carina and right bronchus. Films taken in this position show many rounded and oval densities due to trunks axial to the incident ray. These are usually not confusing in the lower third over the heart shadow, but may be so just to the right of the right bronchus where it leaves the carina. These densities, however, rarely have the granular or stippled quality of calcium infiltration, and they change in quality and contour on slight rotation of the right side forward or backward. If these shadows due to vessels running to the apex prove confusing, the oblique exposures may be made with the right side closer to the cassette changer. The trunks then appear as curving or snarled ascending linear shadows.

Physical Signs. Our experience with physical signs in the diagnosis of tracheobronchial disease has been disappointing. Prolongation of the distinct whispered voice downward was common to the third, and not infrequent to the fifth dorsal spine; but we were unable to account for it on the basis suggested by d'Espine. The level to which it was heard often varied in the same individual depending on whether the head were erect or slightly over-extended, or bent forward, being lowest in the last position. Possibly this is due to some increased conductivity of the tissue between the trachea and the spine. But there was in our cases no definite relation of the sign with the presence of calcium-bearing tracheo-

bronchial glands, and, as noted above, none such could be seen extending to the spine (see Figs. 7 and 8.)

Percussion gave almost equally unsatisfactory results. There was no constant relation between apparent changes of percussion note and a demonstrable lesion.⁹ It is not easy to understand how lesions other than the massive caseation of fatal infantile tuberculosis, which alone, apart from the malignant tumors, protrudes materially beyond the spinal margin, could supply an anatomic basis for changes in percussion. The width of the mediastinal shadow must be considered in relation to type of chest, fat, depth of respiration and cardiac phase. A mediastinal shadow extending uniformly 1 cm. beyond the spinal margin for the length of two posterior interspaces has been seen in the short, thick-set build at about the fifteenth year. We have seen essentially this same mediastinal outline both in normal noncontact children without a lesion and in a child with a calcium-bearing lesion 3 by 3.2 cm. lying behind the trachea and lapping for 1.4 cm. beyond the right tracheal wall. This child had been exposed to a source of infection for one year three years previously.

Nor is there commonly a well-defined basis for those changes in percussion in the interscapular region ascribed to changes in muscle tone. If such changes occur and be referred to reflex effects, one must usually assume that caseation within a gland is the cause. For while caseation involving the gland capsule and spreading to the tracheal wall is not uncommon enough to be a postmortem rarity, neither is it so frequent as to be invoked as explanation in the average clinical case.

Symptoms. We have not as yet been able to recognize a characteristic or definite group of symptoms due to tracheobronchial tuberculosis. For example, the child whose film is shown in Fig. 8 looked well and gave no complaints. Malnutrition and fatigue occur perhaps more often in affected children than in others in the same environmental and sociologic status. Respiratory symptoms have been lacking in cases of uncomplicated tracheobronchial disease. It is essential to rule out parenchymatous infiltration when cough or dyspnea is present. This requires, especially in young children very careful technique. Neither in postmortem material nor in the living have we seen evidence that tuberculous tracheobronchial enlargement may give rise to mechanical stenosis. The areolar tissue about the tracheobronchial nodes and the parenchyma of the lung are very much more easily displaced than the air-passages. Unquestionably, extension of caseation through the gland capsule, if it involves the tracheal or bronchial wall, will cause respiratory symptoms. But in these cases it is reasonable to assign them to the concomitant inflammation. Even evidence of stenosis of branches of the vascular tree has been lacking. When this diagnosis is suggested from the prominence of trunk markings

arising near a calcium-bearing gland, it is well to look closely for infiltration in the lung supplied by the prominent branches. Decreased pulmonary elasticity, with consequent reduction of vibration set up by the pulse wave, is much more frequently a cause of locally prominent trunk markings than is thickening of the trunks, whether by disease of the wall or by increase of content. This, however, is a subject to be dealt with more fully elsewhere.¹⁰

Tuberculin Reaction. The quantitative tuberculin reaction is important at those ages at which it is most desirable to recognize the presence, pathologic condition and significance of tracheobronchial tuberculosis. A full statement of the value of the test is given elsewhere¹ but certain of its correlations which are pertinent in the consideration of tracheobronchial tuberculosis are cited here.

It has been found that, in the urban population studied, marked reactions with the lowest quantity used, 0.01 mg. O. T., are the rule at maturity, but that the younger the child the more often is such susceptibility a result of intimate contact with an open pulmonary tuberculosis. And of those children having the more severe reactions, almost two-thirds showed roentgenologic evidence of the primary complex, in large part lesions involving the glands. From the other point of view, considering the group with demonstrable tracheobronchial lesions, 90 per cent reacted with 0.01 mg. of tuberculin. These facts must be aligned with the evidence cited above, that only the presence of calcium infiltration allowed one to perceive the presence of glandular lesions, and with the observed interval of over three years that usually elapsed between the onset of intimate exposure to a source of tubercle bacilli and demonstrable calcium infiltration of the glands. (Calcium commonly appears earlier in a parenchymal lesion.) Therefore, in infants a tuberculin reaction, especially if intense, is in itself an indication for the institution of every measure calculated to improve the child's condition, and above all to prevent the lodgment of additional bacilli, whether a lesion can be shown or not. As stated above, tuberculous glandular enlargement sufficient to bulge beyond the spine shadow in infants is, in our experience, of fatal import. A working diagnosis and an urgent therapeutic indication is established by the tuberculin reaction alone at this age. A marked reaction to 0.01 mg. of tuberculin in a child under five years is still sufficient to warrant therapeutic and preventive means even in the absence of demonstrable lesion. The presence of a recognizable lesion gravely emphasizes the danger and rarely before the fifth year will the calcium shadow be other than fine and presumably labile (Fig. 9). After the fifth year an intense reaction suggests an active lesion especially if the calcium infiltration casts a soft shadow.

The diagnosis in the individual of tuberculous tracheobronchial disease must rest on a demonstrable lesion, and a definite symptom complex can be discovered only by study of cases presenting such

lesions. If diagnosis is to constitute a basis for adequate treatment, it is essential to seek out the infecting source. Intense tuberculin reactions in several children of the same household may point to an unsuspected or to an apparently arrested source of infection. The prevention of massive or prolonged reinfection is no less essential to the rational treatment of the tuberculosis of childhood than to any radical prophylaxis deserving the name. Comparisons of the incidence and intensity of tuberculin reactions and demonstrable lesions in contact and in noncontact families, point to the paramount influence of contagion on the development of tuberculous disease in children. There is reason to believe that from the latent infections of individuals heavily infected in childhood develops the manifest tuberculosis of young adult life, economically the most wasteful form of the disease and, in its turn, the prolific source of latent disease in others.

Conclusions. 1. Study of postmortem material shows that calcium infiltration is the sole distinctive roentgenographic indication of the site of a lymph node situated within the limits of the mediastinum. Calcium-free glands, however enlarged, fail to cause perceptible intensification of the mediastinal shadow.

2. The protrusion of the mediastinal wall beyond the shadow of the spine and sternum by caseous lymph nodes is rare except in fatal infantile cases.

3. Intrapulmonary glands must contain calcium to be recorded roentgenographically. When they are large, that part of their calcium-free margins which projects beyond the arterial main stem will be recorded by contrast with the pulmonary parenchyma.

4. It appears that reabsorption of calcified caseous necrosis within lymph nodes does not occur.

5. Shadows simulating calcification are thrown by vessels axially radiated.

6. No symptom complex has been found characteristic of tracheo-bronchial tuberculosis. Respiratory symptoms due to uncomplicated tracheo-bronchial disease do not occur.

7. The quantitative tuberculin reaction gives important indications as to the activity of the lesion in the individual. It is of unique value in infancy. It gives indispensable information regarding the source of infection, ignorance of which frustrates alike treatment and prophylaxis of tuberculous disease at its most tractable phase.

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CHRONIC INFECTIOUS ARTHRITIS.

AN ANALYSIS OF 200 CASES

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THE object of this study has been to define more clearly the clinical features of chronic infectious arthritis as distinguished from other forms of arthritis and to evaluate the various measures which have been employed in its treatment. This investigation is based on 200 consecutive cases of infectious arthritis which have come under our observation during the past four years at the Cornell Clinic. In a recent study by the writers¹ of 612 cases of chronic arthritis, 379 fell in the infectious group. The first 200 of the latter form the material for the present study.

In a previous communication² we have described a form of chronic arthritis which is not uncommonly seen in association with the menopause. In that study the conclusion was reached that arthritis of the menopause is probably noninfectious. If certain forms of chronic arthritis are not of infectious origin, it is very important to learn to differentiate them from the infectious type. The theory of focal infection has been so widely accepted that many clinicians now consider all arthritis an infectious disease. As a matter of fact chronic infectious arthritis is a definite clinical entity which can usually be distinguished from other forms of joint disease. Under the term, chronic infectious arthritis, we have included those cases which presented the picture of a chronic proliferative arthritis of distinctly inflammatory character, almost always migratory, and usually associated with one or more foci of infection. Cases

of specific infectious arthritis (gonococcus, tuberculous, staphylococcus, and so forth) have not been included.

Incidence. Chronic infectious arthritis has been by far the most common type of arthritis seen at the Clinic. Of all the cases of chronic arthritis admitted to the Clinic, 62 per cent have been of the infectious type.

Sex. There were 119 females and 81 males. This is in accordance with the findings of other observers who have noted the preponderance of chronic infectious arthritis in the female.

Age. The average age at onset for male patients was 34.5, for females 35.6. The youngest patient was four years of age and the oldest was sixty-one. The incidence of the disease according to decades is shown in the following table:

TABLE I.

Age at onset.	No. of cases.
1 to 10	3
11 to 20	14
21 to 30	62
31 to 40	57
41 to 50	43
51 to 60	21

It will be seen from this table that infectious arthritis begins most frequently in the third and fourth decades. This is in sharp contrast to the age incidence of arthritis of the menopause which occurs nearly always in the fifth or sixth decade.

Races. Practically all races were represented. There was no evidence of any racial predisposition.

Occupation. Most of the women were housewives. Of the 55 males who stated their occupation 33 were engaged in indoor and 22 in outdoor work. Infectious arthritis is apparently just as common in those who are sheltered as in those who are exposed.

Weight. The average weight of the males was 150.5 pounds, of the females 140.1 pounds. The age, height, weight relationship was determined for 59 females. The average age was 34.8, the average height was 5 feet 3 inches, the average weight was 139.9 pounds, as compared with the normal weight of 132 pounds for women of this age and height. The same relationship was determined for 41 males. The average age was 36.9, the average height was 5 feet 7 inches, the average weight was 146.8 pounds, as compared with the normal weight of 151 pounds for men of this age and height. These figures are quite different from those determined for menopause arthritis in which the patients averaged 43 pounds overweight. Generally speaking, individuals afflicted with infectious arthritis do not display such robust good health as those with menopause arthritis.

Etiology. All recent investigators of chronic infectious arthritis are agreed that the disease originates from some primary focus of

infection. Our investigations have led us to the same conclusion. The following table indicates the location of the various foci of infection that were demonstrated:

TABLE II.—LOCATION OF FOCI OF INFECTION.

Tonsils	68	Teeth and cervix	2
Tonsils and teeth	30	Teeth and middle ear	1
Tonsils, teeth, and cervix	6	Colon	7
Tonsils and cervix	5	Prostate	5
Tonsils and prostate	5	Pharynx	4
Tonsils and gall bladder	2	Cervix	4
Tonsils and colon	2	Sinuses	4
Tonsils and sinuses	2	Middle ear	1
Tonsils and osteomyelitis	1	Gall bladder	1
Tonsils, teeth and prostate	1	Pharynx and pyelitis	1
Teeth	21	Cervix, appendix and tubes	1
Teeth and prostate	2	Pharynx and colon	1
Teeth and pharynx	2	Gall bladder and pharynx	1
Teeth and gall bladder	2	None found	18

Infected tonsils were the commonest focus of infection, occurring *either alone or in combination with other foci* in 61 per cent of the cases. Next in frequency were infections about the teeth. Only those teeth were considered as foci of infection which showed severe pyorrhea or apical abscesses by the Roentgen ray. The teeth *alone or in combination with other foci* were the seat of infection in 33 per cent of the cases.

The sinuses were diseased either alone or in combination with the tonsils in 6 cases. The prostate was considered the source of infection either alone or in association with other foci in 13 cases. We were particularly interested in the relationship of gall bladder disease to chronic arthritis. The gall bladder was infected either alone or in association with other foci in 6 cases. Infectious arthritis is probably referable to the gall bladder more frequently than is generally supposed. One of the authors has recently seen 2 other cases of infectious arthritis in which the focus of infection was undoubtedly in the gall bladder. A good many of the cases of infectious arthritis occurring in middle-aged women without demonstrable foci are probably referable to infected gall bladders. Colitis, either of the mucous or ulcerative type, was present in 10 cases. Judging from our own experience the intestine has been overstressed as a focus of infection in arthritis. The incidence of the rarer foci such as the middle ear, female adnexæ, and so forth, can be found in Table II.

From these figures it is evident that the tonsils and teeth are by far the most common site of foci in infectious arthritis. This corroborates the observations of previous investigators. In this connection it is interesting to note that the average age of the onset of arthritis in patients with infected tonsils was thirty;

whereas the average age of onset in those with dental infection was forty-two.

Morbid Anatomy. In this series of cases there have been only two deaths. In neither of these cases were we able to procure autopsy material. From physical examination, however, and from a study of the radiographs it is obvious that chronic infectious arthritis is essentially an inflammatory and proliferative process. We use the term proliferative as employed by Nichols and Richardson³ to describe a pathologic change in the joint structure which is primarily an inflammation of the synovial membrane and the periarticular structures. Because of the fact that many of the patients were seen early before bony changes had taken place, a large number presented only periarticular changes which were apparent on physical examination and also with the Roentgen ray, as a diffuse swelling of the soft parts around the joint. This periarticular infiltration is quite characteristic of the type of arthritis under discussion. Some of the more chronic cases showed bony changes particularly at the margins of the articulating surfaces. Occasionally bony spurs have been found with the Roentgen ray, but undoubtedly, in a large majority of the cases of infectious arthritis the *primary* change is in the synovial membrane and not in the articular cartilages. This is in sharp contrast with the degenerative type of arthritis which almost invariably *begins* as a destructive process in the bone and cartilage of the articular surfaces.

Symptomatology. Patients with infectious arthritis often date the onset of their illness from some disturbance of their physical equilibrium such as an acute infection, exposure to cold, a surgical operation, or a confinement. In taking the histories of patients we were interested in discovering any such predisposing factor which might have precipitated the arthritis. Twenty-nine patients gave a history of a preceding tonsillitis or sore throat; 24 had had a cold or influenzal attack just before the onset of arthritis; 10 others dated their joint symptoms from an attack of rheumatic fever. In 5 cases, arthritis developed after a surgical operation. A large number of patients gave a history of exposure to cold or damp surroundings. In 118 cases no immediate predisposing factor was demonstrable.

Chronic infectious arthritis is usually a polyarticular disease which may involve any joint in the body. It may develop suddenly or gradually. In the present series the onset was sudden in 119 cases and gradual in 81 cases. When the onset is sudden the patient may run an irregular fever, varying from 99° to 100° or even 101°. The disease is almost always migratory in its early stages, jumping about from joint to joint very much like rheumatic fever. After several attacks however, the joints chiefly affected become permanently injured and the process takes on a chronic character. The following table indicates the joints first involved.

TABLE III.—JOINTS INVOLVED.

Joint.	No. of times first involved.
Knee	38
Shoulder	25
Finger	22
Questionable	20
Feet	16
Wrist	15
Ankle	14
Back	10
Elbow	9
Hand	7
Toe	5
Hip	4
Arm	3
Spine	3
Heel	3
Leg	2
Neck	2
Thigh	1
Jaw	1

The knees were the joints first involved in only 19 per cent of the cases. This is in sharp contrast with the menopause type of degenerative arthritis in which the disease made its first appearance in the knees in 84 per cent of the cases.

Occasionally the disease limits itself to only one joint, but in the present study only 2.5 per cent of the cases were monarticular. The number of times each joint was involved is shown in the following table:

TABLE IV.—TOTAL NUMBER OF TIMES THE VARIOUS JOINTS WERE INVOLVED.

Knee	128	Toe	24
Finger	102	Heel	18
Shoulder	87	Knuckle	18
Wrist	74	Neck	15
Ankle	67	Arm	13
Feet	55	Heberden's nodes	12
Elbow	51	Leg	10
Hand	48	Thigh	6
Back	37	Jaw	4
Hip	33	Sternoclavicular	2
Spine	24		

The knees were the most common site of involvement; they were implicated in 64 per cent of the whole series. Fingers and shoulders were the next most frequently affected, 51 and 43 per cent respectively. It is interesting to note that Heberden's nodes occurred in only 6 per cent of the cases, which is in marked contrast with the menopause type of degenerative arthritis in which they occurred in 74 per cent of the series. Of the 102 cases in which the fingers were involved, 58 presented the fusiform finger joint, one of the characteristic features of infectious arthritis.

The patient with infectious arthritis is usually quite uncomfortable. In most cases there is considerable pain, particularly on motion. For this reason the patient is more apt to be seen early in the disease than is the victim of menopause arthritis which manifests itself only as a stiffness of the joints, particularly in the early stages. Many of the patients complain of swelling of the joints affected, and sometimes there is redness and heat as well. As the disease advances, there is considerable disability due to pain on motion and weakness of the muscles from disuse. Unless the disease is checked in its course partial or complete ankylosis may occur in one or more joints.

Physical Examination. Typical cases of chronic infectious arthritis present certain constitutional signs that are striking. They are usually anemic, averaging about 73 per cent in hemoglobin; many of them appear chronically ill and undernourished; some of the patients present marked evidence of loss of weight, particularly those, in whom the disease has lasted for some time. Some of the early cases, however, show excellent nutrition and no anemia. Fever is uncommon when the cases are seen at the clinic but may be present at the onset of the disease.

The examination of the tonsils is naturally of great importance. Infected tonsils as seen so often in young adults may be large, red, and full of pus. Perhaps more frequently, diseased tonsils are small, congested, and partially buried. This type is more common in adults and in early middle age. Either one of these types may contain deep crypts from which pus or cheesy exudate can be expressed. In these cases the fauces of the tonsils are apt to be involved in the infection and present a congested cyanotic appearance. In addition to the infection of the faucial tonsils the patient may show a granular pharyngitis with hypertrophy of the lymphoid tissue.

The gums may show various grades of gingivitis. Pyorrhea may be mild or severe; localized or general. Apical abscesses are found only at the roots of dead teeth.

The examination of the chest is usually negative. We have not seen a single case of infectious arthritis that could be definitely attributed to pulmonary infection. Examination of the heart is usually normal but cardiac lesions are apt to be present in those patients that give a history of acute or subacute rheumatic fever. The abdominal findings are as a rule negative except in the small percentage of cases in which there is infection of the gall bladder or some other part of the intestinal tract. The genitourinary exploration of the male may reveal a swollen, boggy and tender prostate. In the female marked erosions may be found in the cervical mucosa.

In the early stages the joints affected usually present a characteristic appearance. There is more or less swelling of the soft parts and the overlying skin is warm and sometimes reddened. In some cases there is an increase in synovial fluid. The swelling is due for

the most part to the outpouring of inflammatory exudate into the periarticular structures. Tenderness is usually present and is most marked on the lateral aspects of the joints. Motion either active or passive is painful. In the early stages there is no crepitation.

In the later stages much of the swelling disappears. A certain amount of thickening may persist about the joint due to a new growth of fibrous tissue in this region. In the joint itself however the granulation tissue may become converted into adhesions which eventually lead to partial or complete fibrous ankylosis. In those cases in which proliferation of the perichondrium predominates bony ankylosis is apt to occur. Ankylosis is usually associated with considerable atrophy of the neighboring muscles. Sixteen of the present series showed fibrous ankylosis and 6 of the patients were found to have true bony ankylosis.

In this connection it is interesting to note that the longer the duration of the disease the more apt are we to find bony changes present. Only 23 per cent of the cases showed definite bony changes, and their average duration was four years, eight months three weeks, as contrasted with the average duration of two years, six months, in the cases which showed no bony changes. Swelling was present in 51 per cent of the cases. In the patients that are seen early there may be no swelling or bony changes present and the disease may be manifested solely by subjective sensations. In these cases examination of the joints reveals nothing abnormal except possibly slight tenderness on motion. Fusiform finger joints are a common finding in this type of arthritis and when seen are almost diagnostic. They occurred in 58 cases of our series.

Illustrative Case. The following case is a good example of chronic infectious arthritis:

H. S., a man, aged thirty-eight years, whose weight was 125 pounds and height 5 feet 7 inches, had had intermittent pains in the joints for the past twelve years. These pains skipped from joint to joint, especially in the attack which he had suffered eight years before and which had lasted for about one year. He has never had fever and never been confined to bed. At different times his joints have been swollen, red and hot. For the past five years he has had pain, swelling, and stiffness of both wrists. His condition is stationary at present. No history of sore throats or tonsillitis was elicited, but nine months prior to admission eight abscessed teeth were removed. Physical examination reveals a poorly nourished adult, male, 27 pounds underweight; considerable dental repair is present but no pyorrhea. The tonsils are red, ragged, and contain pus. Heart and lungs are normal; abdominal examination negative. Prostatic examination reveals nothing abnormal; examination of the sites of other foci is negative. Locally both wrists

are thickened, slightly tender and warm, and markedly restricted in function. Several fusiform finger joints are present. Wassermann test was negative on two occasions. Blood sugar, 115 mg., uric acid, 3.3 mg.; hemoglobin, 60 per cent; white blood cells, 11,200; polymorphonuclears, 71 per cent; lymphocytes, 25 per cent.

In this case the principal features of chronic infectious arthritis are present. An adult patient, considerably underweight, with marked anemia, gives a history of migratory involvement of the joints and presents upon physical examination polyarticular arthritis with swelling of the various joints and fusiform finger joints. In addition, foci of infection are present.

Laboratory Findings. *Bacteriology.* We have had no opportunity to take cultures from the infected joints themselves. Cultures from the various foci of infection corroborate in general the work of previous investigators. It is interesting to note that cultures from infected tonsils usually yield large numbers of hemolytic streptococci, whereas cultures from apical abscesses almost invariably give pure growths of *Streptococcus viridans* from other foci of infection either type of streptococcus may be obtained. One is forced to conclude from this that both *Streptococcus hemolyticus* and *Streptococcus viridans* can act as the etiologic agents in infectious arthritis.

Serologic Diagnosis. The complement-fixation test as advocated by Burbank and Hadjopoulos⁴ has not been employed in this study. We are therefore in no position to criticize it as a diagnostic measure. On theoretical grounds, however, it would seem to be open to several sources of error. In the first place the authors assume that every case of arthritis is infectious in origin, a point of view which we think is untenable. Furthermore it is quite conceivable that an individual, who at any time had had a streptococcus infection of whatever nature, would have streptococcus-fixing antibodies in his blood as a result of such infection. Since it is extremely difficult to rule out the history of streptococcus infection in any patient the value of the test even when positive is open to question.

Blood Chemistry. In 14 cases the determination of the blood sugar was done. The average finding was 125.3 mg. which is slightly above the normal limit. In 16 patients the uric acid in the blood averaged 3.3 mg. The urea and creatinin in the blood were estimated in a few cases with negative results.

Basal Metabolism. Seven cases had basal metabolism determinations. The findings were entirely negative.

Diagnosis. The diagnosis of a typical case of infectious arthritis presents very little difficulty. The important features that differentiate this particular type from other forms of joint disease are the following:

1. It is more apt to occur in young people.

2. The migratory character of the disease is characteristic.
3. The affected joints are usually swollen and tender.
4. Infectious arthritis is prone to attack the metacarpophalangeal and proximal phalangeal joints.
5. Foci of infection can usually be demonstrated.

Differential Diagnosis. Infectious arthritis must be differentiated from subacute rheumatic fever, a distinction which is not always easy to make. In both conditions the patient may give a history of a preceding tonsillitis followed by an acute arthritis with fever and swelling of the joints. In rheumatic fever however, the temperature is higher, the sweating is more profuse and cardiac complications are frequent. The therapeutic test is valuable. Treatment with sodium salicylate or aspirin usually gives instant relief in rheumatic fever. In infectious arthritis these drugs are practically useless.

Menopause arthritis occurs in obese middle-aged women at or just after the menopause and attacks chiefly the knees and distal phalangeal joints. There is an absence of inflammatory swelling. It is not migratory and foci of infection are usually absent. It may be advantageous to draw a parallelism between these two outstanding types of arthritis.

TABLE V.—DIFFERENTIAL DIAGNOSIS.

	<i>Infectious arthritis.</i>	<i>Menopause arthritis.</i>
Average age at onset	Third and fourth decades	Fifth and sixth decades
Weight	Normal or underweight	Overweight
Blood	Low hemoglobin	Normal hemoglobin
Foci of infection	Usually present	Usually absent
Morbid anatomy	Inflammatory and proliferative changes	Degenerative changes
Joints involved	Any joint in body	Chiefly knees and fingers
Type	Migratory or progressive	Localized
Appearance of joints	Periarticular swelling	No swelling
Special signs	Fusiform finger joints	Heberden's nodes
Roentgen ray	Narrowing and clouding of joint space	Lipping of bony margins

The specific forms of arthritis as well as morbus coxæ senilis and senile arthritis present such characteristic features that there is little difficulty in distinguishing them from the infectious type.

Treatment. The method of procedure in the treatment of these cases has been: (1) The removal of all foci of infection; (2) vaccine therapy; (3) physiotherapy. Medicinal treatment has played practically no part in our therapeutic regime. In the clinic we have not employed foreign protein therapy intravenously for obvious reasons.

Tonsillectomy. Altogether 85 patients (42.5 per cent) in this series of cases were subjected at some time to tonsillectomy. In 9 of these the operation was performed twice. In all, 94 tonsillectomies were done. Strangely enough, 27 patients were subjected

to tonsillectomy before the arthritis made its appearance. In these cases obviously the tonsils were not the focus of infection. The following table shows the relationship of tonsillectomy to the duration of the disease:

TABLE VI.—RELATION OF TONSILLECTOMY TO DURATION OF DISEASE.

<i>Duration of disease..</i>	<i>No. of cases.</i>
Tonsillectomy before onset	27
6 months or less	18
6 months to 1 year	10
1 year to 2 years	9
2 years and over	26
Relation unknown	4
Total	94

Nearly half of the patients with chronic arthritis waited two years before having their tonsils removed.

Teeth were extracted because of apical abscesses in 21 cases. A considerable number of patients were treated for pyorrhea. Eight patients received prostatic massage and bladder irrigations. Five cases were treated for disease of the cervix. Four cases had infected sinuses punctured and irrigated. Only 1 gall bladder was removed and the middle ear received treatment in 2 cases. In a considerable number of cases the removal of foci was supplemented by colonic irrigations.

Vaccine Therapy. Vaccine therapy was used in the treatment of 39 cases. In only a few of the cases did this constitute the sole method of treatment. As a rule this form of therapy was used only after a thorough search for foci of infection. A polyvalent Streptococcus hemolyticus vaccine with a concentration of 4 billion organisms per cubic centimeter was used in 27 cases. The initial dose was as a rule 0.2 cc. The vaccine was administered subcutaneously twice a week until ultimately the patient received 1 cc. at each injection. Autogenous vaccines prepared from the deep crypts of the tonsils directly after their removal, were given in 7 of the cases. A polyvalent Streptococcus viridans vaccine was used in 2 cases and Bacillus coli and Staphylococcus aureus vaccines were used in 1 case.

Physiotherapy. Physiotherapy was used as an adjuvant in the treatment of almost every case. Baking, massage and diathermy were the methods of treatment most frequently employed. As a rule this treatment was not used during the period of active inflammation in the joints but was reserved for the resolution of exudates and the restoration of function.

Period of Observation. In this series of 200 cases, 57 patients were sent to the Clinic for diagnosis only; 143 received treatment. Of the latter group, 92 patients were under our observation for a period of time lasting from three months to three years. Thirty-

seven cases were treated less than three months and the duration of treatment in 14 cases is not known.

Results of Treatment. The duration of the arthritis when treatment is instituted is a determining factor in the results obtained. In the following table this relationship is clearly brought out.

TABLE VII.—RELATION OF DURATION OF ARTHRITIS TO RESULT OF TREATMENT.

Results of treatment.	No. of cases.	Average duration of disease when treatment started.
Recovery	20	1 year 1 month
Much improved	39	3 years 10 months
Improved	43	4 years 5 months
Unimproved	39	5 years
Died	2	1½ years and 3 months
Total	143	

It is clear that results in the treatment of chronic infectious arthritis depend as much on the duration of the disease as they do upon the therapy employed. The significance of this fact has not been sufficiently emphasized. It may be laid down as an axiom that cases seen within the first year of the disease have an excellent chance of recovery under suitable therapy and that cases which have lasted five years and over present almost insuperable difficulties in their treatment. It would be well for both patient and physician to realize that the treatment of arthritis no less than the treatment of tuberculosis should be instituted early in the course of the disease. The most painstaking search for, and removal of foci in late cases does not give the results that are obtained in cases that have lasted only six months or less. The following table shows the results of treatment in cases of less than six months duration:

TABLE VIII.—RESULTS OF TREATMENT IN EARLY CASES.

Total number of such cases	36
Cured	10
Much improved	11
Improved	8
Unimproved	6
Died	1

It is significant that 82 per cent of these cases were either cured or improved while on the other hand an analysis of the unimproved cases shows that the average duration of the disease when treatment was instituted was five years.

The duration of treatment in the unimproved cases averaged three months (most of them coöperated). Thirteen tonsillectomies were performed in this group without success. Extraction of teeth was done in 7 cases. Streptococcus hemolyticus vaccine was given in 6 cases. Prostatic massage was employed in 1 case and

most of the patients received physiotherapy. Failure to improve under treatment was undoubtedly due to the long-standing processes in the joints and the presence of secondary foci of infection.

Tonsillectomy. Of the 65 tonsillectomies that were done after the onset of arthritis only 29 were cured or showed improvement. It is only fair to state that 13 of the remaining 36 tonsillectomies were performed after the disease had been present for five years. In those cases in which the tonsils were the foci of infection and their removal was effected within the first six months of the onset of the arthritis our results have been uniformly good. It has been our experience that the full effect of tonsillectomy is not obtained until three to six months after operation.

Results of Extraction of Teeth. Of the 21 cases that had extractions done, 7 were cured, 3 much improved, 3 improved, and 8 unimproved. Sixty-two per cent of the series were cured or improved by this method of treatment.

Results with Vaccine. It is difficult to evaluate the role that vaccine played in the treatment of these cases, as it formed only a part of the general therapeutic régime. Our experience with *Streptococcus hemolyticus* vaccine has not shown uniform results. A few of the patients have responded favorably for a short time, but the vaccine itself seems to have no specific action and does not appear to be superior to any other foreign protein in its effects. Autogenous vaccine has been used in only 7 cases, with apparently marked improvement. But as these patients had all been subjected to tonsillectomy before the vaccine was employed it is difficult to separate the effect of vaccine from the end-results of tonsillectomy.

Physiotherapy. In our experience physiotherapy (radiant heat, 15-20 mm.; diathermy, 20 minutes, massage and passive movements, when indicated) has been a valuable aid in the treatment of infectious arthritis. It may act favorably in two ways, first, by accelerating the absorption or removal of exudates, second, by hastening the return of function in the partially ankylosed joints. It is obviously not indicated until after foci of infection have been removed.

Summary. 1. Infectious arthritis is primarily a disease of early adult life.

2. The tonsils and teeth are the commonest foci of infection.

3. In young people infected tonsils are responsible for a high percentage of the cases. In older patients infected teeth are more apt to be the etiologic factor.

4. The pathologic changes are of a chronic inflammatory and proliferative character, terminating often in ankylosis and deformity.

5. Clinically the disease manifests itself as a migratory, poly-articular affection of the joints characterized by swelling, pain, and stiffness of the parts affected. The fusiform finger joint presents the typical picture.

6. Success in treatment is dependent upon a relentless search for foci of infection, and their prompt removal early in the course of the disease.

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MYOSITIS OF RECTUS ABDOMINIS MUSCLES CONTRASTED WITH ACUTE INTRAÄBDOMINAL CONDITIONS.

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A SEARCH of the literature on myositis of the abdominal muscles reveals very little which may be interpreted as a differential diagnosis between this condition and those of acute intraäbdominal origin. In this location myositis assumes considerable importance because of its possible confusion with suspected intraäbdominal disease. There is a certain percentage of cases with acute abdominal pain in which myositis is the causative factor, as shown by examination and the response to salicylates. The purpose of this paper is to review the symptoms of abdominal myositis in contrast to those of intraäbdominal conditions and report 2 cases illustrating the typical syndrome. A theoretical discussion of the probable cause of pain in myositis and perimyositis is also given.

The earliest and most complete consideration of myositis from this standpoint was given by Hoover.¹ He pointed out that an inflamed muscle, unlike most structures which are tested for the seat of pain, gives no pain on functional employment if the inflammatory process is within the muscle sheath. The lack of pain on functional employment is explained by the structure of the muscle. It consists of a sheath containing a semiliquid substance in which pressure is transmitted equally in all directions during activation in the same manner as pneumatic or hydrostatic pressure. Since pressure is applied in this manner within the muscle sheath there can be no distortion of its component parts. However, when an inflamed muscle is palpated or stretched, there is distortion of its structure and pain results. The same principle may be illustrated in the case of a subcutaneous abscess. There may be pain due to tension on the walls of the abscess from within and to barometric pressure on the skin surface, but it is not nearly so intense as that produced by distortion of the walls by manipulation.

It is to be noted that perimyositis gives pain on activation of the involved muscle. In such a case adhesions between the sheath and surrounding tissues give opportunity for distortion of the inclosed muscle. Friction between sheaths of contiguous muscles, the seat of perimyositis, may also be the cause of pain. The mechanism of pain production in such pathological conditions is not entirely clear. It cannot be due to the same sort of intense stimulation of nerve ending, for instance, as results from the application of a hot object to the skin surface. Therefore since thermal stimuli can be disregarded it must in all probability be due to mechanical factors. A friction rub immediately suggests the movement of one roughened surface over the other but this alone cannot explain pain nor on the other hand does inflammation of the otherwise smooth surfaces explain it. It seems logical that as a result of inflammation there is a distortion of tissues resulting in compression and stretching and thereby irritation of nerve endings. A normal muscle may be stretched within limits without pain, but if a constant traction is maintained for a long period of time, pain results. Therefore it seems essential to include the time factor as well as distortion in the production of pain.

There are cases of myositis in which there is complaint of some pain on activation, but not nearly as much as on mechanical distortion by palpation or stretching. It has been observed that such cases have had palpable masses in the muscle which varied in size from a small pea to large tumors, 5 to 6 cm. in width and extending transversely across the muscle. One patient had such areas in the upper part of both gastrocnemius groups, which were painful when the muscles were activated and also when at rest, but the pain was accentuated to a marked degree on stretching or palpation. The difference between such a case and one in which nodules are not palpable and there is no pain on activation is probably a matter of degree and duration of involvement. A small area of inflamed muscle cannot of itself produce much distortion, but a large tumor may so disturb the structural units of the muscle that pain becomes a constant symptom even when the muscle is relaxed. When the shoulder, neck and back muscles are involved the problem of diagnosis is much simpler than in the case of the abdominal group. The procedure in examining the latter group is first to palpate the abdominal wall thereby determining the presence or absence of rigidity, muscle spasm, and tenderness. The patient is then asked to bear down and the abdominal wall is palpated while under tension. If peritonitis is the causative factor the pain on palpation will be less in this than in the first procedure, and if myositis is the cause it will be accentuated.

In addition to this finding a sensory examination is of importance. There is never any disturbance of sensation of the skin overlying a muscle, the seat of myositis, but there is a change over an area of peritonitis. This latter fact was pointed out by Gammon² in 1912

when he demonstrated sensory disturbance of the skin over an acute appendicitis. He found tenderness on pressure over the appendix, but also a diminished sensibility to heat, cold, and the vibration of the tuning fork and attributed this to the inhibiting effect of visceral pain on other sensations in the same segment of the spinal cord. These findings were constant in cases of acute appendicitis when seen early in their course. If pain had subsided in such patients the sensory disturbances had also disappeared and operation showed a gangrenous or suppurating appendix. The explanation offered in such a case was that engorgement or gangrene had rendered the visceral peritoneum anesthetic which effectively blocked sensation to the cord and thereby removed the inhibitory influences on the sensations of heat, cold and pallesthesia to the segmental distribution of the skin. The same mechanism resulted in a diminution of pain by the application of an ice bag over the appendix which by intense stimulation of the skin inhibited pain from the appendix which was in the same segmental distribution. Thus, since inflamed peritoneum gives disturbed sensation, unless acute engorgement or gangrene is present, and myositis never gives such findings, sensory disturbances become an important factor in differential diagnosis.

Two cases have recently come under our observation, one with symptoms suggesting acute cholecystitis and the other acute appendicitis, both of which proved to be acute rheumatic myositis of the rectus abdominis muscles. A survey of the records of the Lakeside Hospital shows only 3 more cases which were undoubtedly of the same type. We do not consider this an indication of the extreme rarity of the condition, but rather failure of recognition in perhaps many more cases. For this reason a report of 2 typical cases may be of value.

It will be noted that the diagnosis in these cases was based on the following findings:

1. Activation of the rectus muscle was painless.
2. Stretching of the affected muscle caused exquisite pain.
3. Palpation of the relaxed muscle gave little pain, but of the activated muscle a considerable degree of pain.
4. There was no disturbance of sensation over the affected areas.
5. The administration of salicylates gave relief in a very short time.

Case Reports. CASE I.—M. L., a female, aged sixteen years, five days prior to admission had a dull aching pain in the right lower quadrant of the abdomen and also in both knees and shoulders. There was no nausea, emesis or diarrhea, but there was anorexia.

Past History. There had been an attack of acute rheumatic fever one year prior to this admission but, in the intervening period, there had been no symptoms of myocardial insufficiency. There

had been only one menstrual period, but there was no history of exposure to venereal disease.

Physical Examination. The temperature, pulse, and respirations were respectively 39.4°, 104 and 24. Both knees were swollen and tender with an elevation of the local temperature. Palpation of the relaxed abdominal wall revealed no muscle spasm and only a moderate degree of tenderness over the lower half of the right rectus muscle. However, when the muscle was stretched or activated, palpation gave very severe pain. There were no disturbances of sensation over the painful area. Rectal examination was negative. The cardiovascular system gave the findings of a well-established aortic insufficiency.

Laboratory Findings. On admission, January 10 at noon, the white blood cell count was 11,900. At midnight it was 10,800, and at 5 A.M. the next morning 11,600. A differential blood count showed 80 per cent polymorphonuclear leukocytes. The urine was negative for blood and showed only an occasional pus cell. A blood culture gave no growth in forty-eight hours.

Course. Cincophen was begun at 6 P.M. on January 10, in doses of 20 gr. every three hours and discontinued when nausea and emesis resulted at 9 A.M., January 11, when a total of 80 gr. had been given. The symptoms had cleared up so completely that the patient refused to stay longer than three and a half days, at which time, however, there was no tenderness over the right rectus muscle. The temperature fell to normal in twelve hours and continued normal.

Diagnosis. Subacute rheumatic fever, rheumatic myositis, chronic endocarditis with aortic insufficiency.

CASE II.—W. R., a man, aged forty-two years, six months prior to admission began noticing periodic attacks of dull aching pain in the epigastrium, not related to meals and with no associated nausea, emesis or eructation of gas. The appetite remained good. Two weeks prior to admission there was an onset of one and then periodical attacks, which involved the entire upper abdomen. On this occasion the pains were so severe that relief could not be secured without flexing the thighs on the abdomen. There was no gastrointestinal disturbance of any sort, and no constipation or abnormality of stools. There was no urinary disturbance and no fever. The patient had worried considerably and had lost about 15 pounds.

Past History. Entirely negative.

Physical Examination. The temperature, pulse and respirations were normal. The patient was lying in bed with thighs partly flexed on the abdomen. There was no icterus. The heart and lungs were normal. Abdominal examination showed no distention, visible peristalsis, palpable organs, tumors, or free fluid. The maximum points of tenderness were: (1) In the left lower quadrant

at the outer border of the rectus, 3 cm. below the umbilicus; (2) near the costal margin in the mid portion of the rectus muscle on both sides. Deep pressure gave muscle spasm and some pain over these areas, but stretching and distortion of the activated muscle very severe knifelike pain. There were no sensory disturbances. The prostate was slightly enlarged, but rectal examination was otherwise negative.

Laboratory Data. Roentgen ray plates of renal and gall bladder regions showed no calculi. The white blood cell count was 8000. The urine was negative and blood plasma not icteric.

Course. In a few hours after admission the patient was started on a course of cincophen, 15 gr. every three hours. Twenty-four hours later after 150 gr. had been given there was almost complete relief from abdominal pain and the patient had the first night of undisturbed sleep for two weeks. At this time palpation of the abdomen failed to elicit muscle spasm, but there was still slight tenderness to firm pressure midway between the umbilicus and xiphoid process. Activation gave no pain, but there was slight pain with stretching of the muscles a slight degree. During the next four days 640 gr. of sodium salicylate was given and the patient was discharged free of symptoms and signs.

Diagnosis. Myositis of rectus abdominis muscle.

Summary. 1. Two cases of myositis of the abdominal muscles are reported.

2. The literature on rheumatic myositis is reviewed.

3. The points in differential diagnosis between myositis of the abdominal muscles and intraabdominal conditions are contrasted.

4. The probable cause of pain in myositis and perimyositis is discussed.

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THE MANAGEMENT OF THE CIRCULATION IN MYXEDEMA.

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ARTICLES in the recent literature by Fahr,¹ Christian² and Willius³ have prompted us to the further study of the subject. Fahr concludes there are definite objective signs and subjective symptoms

of heart failure which are characteristic of myxedema and which do not respond to digitalis and rest but are relieved by thyroid medication. He cites a case and recommends thyroid extract for cardiac decompensation in myxedematous patients. Christian, stimulated by this article, reviewed the subject with a study of several cases and summarized as follows: "Patients with myxedema frequently have symptoms and physical signs of circulatory insufficiency. This whether due to thyroid hypofunction or a coincidental disturbance, must be taken into account in planning treatment, because, when thyroid is given in sufficient amount to elevate metabolic rate and cure myxedema manifestations, increased work is thrown upon the heart. This burden is increased if anemia of marked degree is present. To meet it the heart must be able to respond by increasing its work. To do so may require digitalis and other cardiac therapy prior to or during the giving of thyroid extract. To neglect the circulatory element in the treatment of the clinical situation may result in discomfort or disaster from circulatory failure." Willius in a review of 162 cases thinks a definite cardiac syndrome characteristic of myxedema does not exist.

The case which we are reporting with autopsy records and conclusions may serve as a case in point and is further justified by adding to the literature data concerning multiple thrombus formation in the larger bloodvessels.

Case Report. Mrs. G. M., housewife, aged forty-five years, widow, was admitted to the University Hospital (No. 18299) November 7, 1925. During childhood she had measles and whooping cough; at the age of ten years she suffered an attack of typhoid fever, and one year later rheumatism at which time she was confined to bed for four months, and suffered with stiff, painful joints intermittently for the four years following. Her menstrual periods which began at the age of seventeen years had always been scanty and quite irregular. The last menses were in May.

At the age of eighteen years relatives noticed she lacked ambition, her speech became slow, and she tired easily. Her features gradually changed, the face broadened, the eyes and face became puffy, the hair grew coarse, and the skin was thick and scaly. A hypothermia developed and the patient chilled easily. She could work in the field on a hot day quite heavily clothed without perspiring. This condition continued to the present time and although several doctors were seen for miscellaneous ailments, none made a diagnosis of myxedema, and no therapy was instituted. The myxedema had been progressing for twenty-seven years. She more recently developed shortness of breath on exertion, sinking spells, and pain through the upper abdomen radiating to the chest and shoulders rather definitely, but more marked on the right. The pain was

paroxysmal but on account of the apathy its exact nature could not be determined.

On physical examination of the patient, all the characteristic findings of a well-advanced case of myxedema were present and will not be considered in detail. The apex beat was found in the anterior axillary line at the sixth interspace. There was a systolic murmur present, best heard at the apex. The abdomen was slightly tender along the right costal border. The liver was barely palpable. The external genitalia were poorly developed and the uterus was of the small infantile type. The reflexes were sluggish. The blood pressure was systolic, 110; diastolic, 72; pulse rate, 72; respirations, 22; temperature subnormal.

The urine was negative; blood nonprotein nitrogen, 30 mg.; blood sugar, 118 mg.; red blood cells, 3,700,000; hemoglobin, 70 per cent; white blood cells, 6000; blood platelets 230,000; clotting time six minutes. The basal metabolic rate was - 30. The Roentgen ray examination of the teeth showed deep pyorrhea with some bone absorption. The heart shadow was enlarged 4 + to the left and right and the gastrointestinal radiograms were negative.

A diagnosis of myxedema and cardiac hypertrophy with slight decompensation was made, and on November 10 the patient was put on a beginning dose of thyroid (5 gr., t. i. d.) put to bed, and kept under close observation. On the fifth day, in spite of the complete rest, it was evident that the decompensation was increasing and edema appeared over the sacrum. The thyroid extract was decreased to gr. i, t. i. d. The signs of hypothyroidism became less marked. The heart action seemed better and the edema had disappeared from the sacrum. November 21, the thyroid was increased to gr. ii, t. i. d. On November 26, the patient complained of pain in the left side of the neck. An examination revealed a thrombus in the left external jugular vein extending upward for about an inch. The temperature was normal. Several days later the left forearm and hand became numb, cold, bluish and very painful. The pulse could not be felt at the wrist but was present in the brachial artery. A line of demarcation had formed about midway up the forearm. The temperature was normal; white blood count 15,800; the blood cultures repeatedly were negative. December 2 the patient had a slight febrile reaction (100°), the respirations were increased and on examination of the left lung revealed rales and evidences of consolidation in the right lower lobe. The thyroid medication had, of course, been stopped and digitalis therapy instituted. The lung lesion gradually cleared up. A dry gangrene with a definite line of demarcation 4 inches below the elbow had developed in the left forearm. On December 8, there was a left femoral thrombosis followed the next day by a right femoral thrombosis, and on December 10 a thrombosis of the superficial veins on

the medial aspect on the right arm, and in the right external jugular which receded in a few days. By December 26 the jugular veins had softened, the swelling left the legs, and the general condition was much better, and the left arm was amputated by Dr. Jonas just below the elbow under local anesthesia. The stump healed slowly.

The patient remained in the hospital until her death from cardiac failure April 24, 1926. During this time she became markedly decompensated with the slightest effort, or with the institution of thyroid therapy which would be started at intervals and on account of the increase in cardiac symptoms would be discontinued.

Autopsy. An extract of the autopsy record made by Dr. Miller of the pathology department is as follows:

The body is that of a well-nourished and fairly well-developed white woman. The hair is thin, dry, and coarse and the skin over the entire body is thick, dry and scaly. There is no hair in the axilla or pubic regions. The left arm has been amputated just below the elbow and the stump is well healed. The right lower extremity is swollen. The teeth are separated.

Grossly the thyroid weighs 9 gm. and is of the consistency of connective tissue. The sectioned surface reveals small irregular masses of mahogany-brown tissue. The connective tissue of the neck and the vascular compartments of each side are firm and dense. Both external jugulars are thrombosed but soft and pliable. The internal jugulars and carotid arteries are patent. There is an old, firm thrombus in the left brachial artery about 6 cm. from the stump. The veins of the left arm are patent.

The heart weighs 475 gm. The right auricle is filled by an old brownish-colored pliable clot. There is a large mural thrombus in the tip of the left ventricle. The coronary vessels are sclerosed and almost occluded near their orifices. The larger branches, however, are free from thickening and other signs of sclerosis. The right ventricle is about twice normal thickness. The endocardium is thickened and light colored. That of the left ventricle is unusually firm and thick, and in underlaid by a light-colored, firm zone of muscle tissue.

Microscopically, the sections of the veins show them to be filled with organized and canalized thrombi. There is considerable damage to the wall of the vein and the perivenous tissue scarred. The thrombus of the brachial artery is organized and canalized. There are no signs of infection in the arterial wall. The mural thrombi of the heart are partially organized. There is necrobiosis of the heart muscle near the endocardium of the left ventricle. Connective tissue is increased, dense and hyalinized. There is no sclerosis of the branches of the coronary vessels. The aorta and large vessels contain typical changes of arteriosclerosis, senile type. The thyroid is almost completely destroyed by slowly progressing,

destructive change. The colloid is small in amount and that present is coarsely granular, and being attacked by phagocytes. There are only a few nests of acini composed of large epithelial cells with dense nuclei. The cytoplasm takes a dense eosin stain. The acini apparently shrink in size, the cells become deranged, degenerated and die. At the periphery of the small epithelial masses there is a dense leukocytic infiltration in which lymphocytes are arranged in follicle formation. Beyond this zone of the gland is old, dense, connective tissue in which there are a few infiltrating leukocytes of all types. Sections of all viscera show many masses of streptococci filling small arterioles. There is no reaction around them.

The section of the skin contains one hair and no sebaceous glands. The sweat glands are small and atrophic. The corium stains faintly and is edematous. The arterioles of the skin are thick and vacuolated. There is a diffuse and moderate infiltration by leukocytes, most of which are polymorphonuclear.

Conclusions. It is quite evident that thyroid medication used in the treatment of myxedema in sufficient dosage to cure myxedema manifestations and raise metabolism will throw sufficient strain on the circulation to increase a cardiac decompensation. We think the damaged heart should be built up with cardiac therapy before thyroid extract is administered.

In the case reported the changes in the heart muscle are believed to be the result of coronary sclerosis. In this instance the sclerosis is in the main branches only. In spite of the attack of rheumatic fever at the age of eleven no active heart lesion of rheumatic fever was found, and the principle tissue changes of the heart do not suggest it. The sclerosis may be due directly to thyroid insufficiency.

The mural thrombi are the result of myocardial and endocardial damage. The thrombus in the brachial artery is the result of an embolism from the mural thrombi with the following organization and canalization. The venous thrombi are not explained. They may be due to a slowing of the circulation and, as is commonly the case, form in larger vessels due to eddying of the blood at the periphery. In the literature, the external jugular veins are the usual site of formation of this type of thrombus. The damage to the venous walls may be interpreted as the result of infection, but it may also be the result of the reaction accompanying thrombosis.

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STUDIES IN URTICARIA. I. WHEEL PRODUCTION THROUGH
INTERNAL CHANNELS.

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Introduction. It is now universally accepted that the wheal, the clinical manifestation of urticaria, is an affection of the skin, mediated by principles derived from two different sources, external or local, and internal or constitutional. Wheals of the former group are produced by the bites or stings of various insects, and by various physical, chemical, or traumatic agents. Among the internal or constitutional causes may be mentioned hypersensitiveness to foods, drugs, and sera, intoxications, infections, metabolic and nervous disturbances, etc.

Up to the present time, the wheal of external origin has been the basis of investigation in most of the experimental studies of the skin manifestations of urticaria. Wheals have been produced locally on the skin, by applications of various physical, mechanical, and chemical agents, and also by intradermal injections of various substances. Probably the earliest record of such work is that of Philippson.¹ Working both on animal and human skins, he produced wheals with morphin, codein, peptone, and so forth, which he inserted into the skin by means of fine capillary tubes. His work was confirmed by Török and Hári² who used, in addition, a number of other drugs. Jadassohn and Rothe³ experimented with morphin wheals produced by the scarification method. Eppinger,⁴ using the same technique, was the first to employ histamin in the production of wheals. Sollmann and Pilcher,⁵ by means of the scarification and mucuna* methods, produced wheals with a number of drugs, including histamin, morphin, peptone, and so forth. Lewis and Grant⁶ made an admirable study of wheals produced by pricking the skin upon which a drop of histamin solution had been placed.

The intradermic method of wheal production was adopted by Pilcher and Sollmann⁷ in their study of morphin wheals. They concluded that race (white or black), age, and sex, did not influence

* Mucuna ("Cowhage;" "Cowitch") consists of the fine stiff hairs of a leguminous seed pod. When gently rubbed on the skin, pruritus with or without erythema is produced. Rubbing the solution of the drug on this area results in the formation of a wheal.

either the size or severity of the reaction. Pilcher⁸ studied wheal formation by the intradermal injection of codein in a series of infants with nephritis, cardiac compensation, leukemia, cretinism, myxedema, scleroderma, and⁹ in rickets and spasmophilia. Except in edematous and sclerotic skins, the wheals did not vary.

Mechanical and physical agents, such as stroking, heat, puncture, scratching, suction, and so forth, were employed for wheal production by Ebbecke,¹⁰ Lewis,¹¹ and Lewis and Grant.⁶ These workers not only produced wheals, but made some interesting observations on certain physiologic factors affecting the wheal in its formation.

It is to be noted, therefore, that up to the present writing, all investigators have produced wheals by the direct application to or into the skin of various agents, either chemical, physical, or mechanical. The experimental production of wheals through internal channels had not, as yet, been accomplished. The writers have, however, devised a technique, based on an immunologic principle, by which such wheals may now be produced at will, on the skin of almost any individual. The mechanism of this reaction, it is believed, simulates that of an urticaria of internal origin. It is probably a reproduction of wheal formation as it occurs in urticaria due to food hypersensitiveness, the type most commonly encountered by the clinician.

Immunologic procedures for wheal production have not previously been employed to any considerable extent in the experimental study of urticaria. The reactions described by Duke¹² can hardly be considered of such nature, since they are the result of the direct action of physical agents, such as light, heat, cold, freezing, and so forth, on a sensitive skin. The usual skin tests for hypersensitiveness, which are now generally employed, either with the scratch or intradermal method, also furnish wheals of external origin, but necessitate for their production an additional constitutional factor in the form of skin hypersensitiveness. This immunologic method of wheal production, however, has not been extensively utilized in urticarial studies.

The immunologic principle on which this investigation is based is an outgrowth of the work of Prausnitz and Küstner,¹³ De Besche,¹⁴ Coca and Grove¹⁵ and others. These workers have shown that an intradermal injection of certain hypersensitive patients' sera into the skin of almost any individual, temporarily sensitizes that site to the same substance to which the patient is sensitive. A positive reaction, a wheal, can be elicited by the intracutaneous test of these sites with the offending substances.

It was while working on one of the phases of this question that one of the writers (M. W.)¹⁶ found the basis for the present study. It was observed that, with the sera of certain food-sensitive patients, the positive skin reaction, the wheal, could also be elicited at a passively sensitized site in most individuals by the ingestion of the

offending food.¹⁷ In other words, by injecting certain hypersensitive patients' sera into the skin of the average individual, and, under proper conditions, feeding him the specific offending food, a wheal can be elicited at the sensitized site.

This specific wheal-inducing property is not present in the sera of all hypersensitive patients. To date, only four such sera have been found. These were obtained from patients who give very marked skin reactions to certain foods by dermal testing, and clinically manifest their sensitivity by asthma and skin lesions. The history of two of these patients is here submitted.

CASE I.—M. K. is a male child, aged two and a half years. The father has asthma. The child has had asthma since he was one and a half years of age, and has had "eczema" or "hives" more or less constantly since he was three weeks old, but is worse in the summer. The asthma attacks occurred at least once a month, lasting two or three days, preceded and accompanied by coryza and rhinitis. During the attacks the skin condition became much worse and the body was covered with a diffuse erythema, wheals, and circumscribed edematous areas, and was markedly pruriginous. Between the attacks, the child showed a generalized eruption of numerous discrete pinhead to pea-size pink papules, many with scratched off tops. Some were secondarily infected from scratching.

On direct skin testing, positive reactions were obtained with cereals, egg, chicken, lamb, mustard, flaxseed and nuts. Of these the egg reaction was found to be the most significant. The serum of this case was the one employed in the subsequent studies of wheal production by egg ingestion.

CASE II.—J. M. is a female child, aged five years. There was no family history of hypersensitiveness. She was breast-fed, and at three months of age, developed "eczema" of the face, which lasted about three months. It promptly cleared up following local treatment and the elimination of fish, sweets, cream and chocolate from her mother's diet. When the child was about a year old, her mother noticed that mere contact of the child with fish produced a violent attack of urticaria. Fish in every form was therefore excluded from the diet. Asthma developed about two years ago, but attacks have been at long intervals, and usually following an acute bronchitis.

On direct skin testing, the patient gave very marked positive reactions to all fish and shell fish. The serum of this case was the one employed in the subsequent studies of wheal production by the ingestion of fish.

Technique. 1. *Preparation of the Serum.* To obtain serum, vein puncture is employed, under the usual aseptic precautions. The blood is drawn and mixed with a sterile citrate solution, to yield a

final 1 per cent concentration of the citrate. Instead of the citrated solution, the blood may be defibrinated by whipping. After it is rapidly centrifuged, the serum is removed, and then passed through a Berkefeld filter for sterilization. The serum so obtained may be used in full strength or in various dilutions. If bottled under sterile precautions (without preservative) and kept in the ice box, it retains its potency for more than six months.

2. *Local Passive Sensitization of the Normal Skin.* The skin site on the subject chosen for study is cleansed with alcohol, and $\frac{1}{20}$ to $\frac{1}{50}$ cc. of the sensitive serum, concentrated or in dilution, is injected intradermally, with the technique employed in the usual intradermal skin tests. Sufficient time is then allowed to elapse for complete disappearance of all signs of irritation, resulting from the trauma of the injection. A control, by the intradermal injection of any serum not sensitive to the specific offending food, may be employed on another site, using the same technique. It is important that the food with which the subject is to be tested should be excluded from his diet on the day of sensitization.

3. *Induction of the Wheal.* The wheal is induced by feeding the specific offending food. This is best accomplished after an abstinence from food for a period of six to eight hours, and is therefore usually most convenient in the morning, the subject having been locally sensitized on the previous day.

The offending food should be taken raw. With the egg serum, one egg, well-beaten, slightly flavored to taste, is usually employed. With the fish serum, about 50 gm. of raw salted herring is ingested. Changing the nature of the food by heating, boiling, baking, canning, and so forth, may diminish or prevent the reaction.

Within three minutes to two hours after eating the offending food, a wheal, the typical characteristic phenomenon of urticaria, forms at the sensitized site. Pruritus is usually the first symptom, soon followed by an erythema, and then the edematous wheal gradually develops. The time of onset, size, and intensity of the reaction is variable with the individual, and depends upon several factors, the chief ones of which are: (1) The amount, dilution, and nature of the sensitizing serum employed; (2) the ability of the subject to accept passive transfer of local sensitivity (about 90 per cent of normal individuals;¹⁷ (3) the ability of the subject to absorb certain incompletely digested or raw proteins from the digestive tract (about 90 per cent of normal individuals¹⁷).

The reaction is a specific one. It develops only at the passively sensitized site, and only after the ingestion of the specific offending food. One wheal formation usually completely desensitizes the site. All control sites sensitized at the same time with other sera remain unaltered. Passively induced local sensitivity may persist from several days to a month of more¹⁵ provided the offending food is excluded from the diet.

The reaction has been elicited in more than 90 per cent of over 100 subjects tested to date. The complete reaction, with all its variations in time of appearance, size, intensity, duration, and all other factors concerned in its development, both in normal and abnormal skins, will be the subject of subsequent communications. The reaction as an index to specific protein absorption is also being investigated, and these results will be published at some future date.

Discussion. The technique, which has just been described, involves an entirely new principle for wheal production in the study of urticaria. It reproduces at will, in almost any individual, the wheal of a constitutional urticaria in a natural way. The factor which induces the formation of the wheal gains access to the sensitized site in its natural form, and through natural channels.

The complete unaltered development of the wheal may be studied in its progressive stages from its onset with pruritus, then erythema, and finally, wheal, together with its retrogressive changes to normal. There are no local traumatic changes at the sensitized site immediately preceding the reaction, which may mask the early symptoms of the developing wheal. Local sensitization may be performed days or weeks before the offending food is eaten, so that any slight traumatic changes that may be produced at the localized site by sensitization have completely disappeared before the wheal is produced. This is in contrast with the older methods, which depend on some form of immediate and local excitation for wheal production.

Another advantage of the technique presented is the fact that it is harmless. With it, any number of wheals may be produced simultaneously on one subject. In the thousands of times that wheals have been produced in more than a hundred subjects irrespective of age, even in infants, there have been no mishaps or untoward results. This method eliminates the dangers of cumulative action or intoxication which accompany the use of powerful agents, such as morphin, histamin, and so forth in wheal production. It also makes unnecessary the employment of hypersensitive patients as subjects—a procedure which is always accompanied by the possibility of a constitutional reaction when the patient is tested with the specific offending antigen.

The single disadvantage in the entire procedure is the difficulty in finding the serum. Once the proper patient has been secured, however, serum may be taken from time to time and a generous supply assured.

Summary. 1. A summary of the previous work on experimental urticaria is presented, showing that all previous methods of wheal production employed various physical, mechanical, and chemical agents, locally applied, to produce a wheal.

2. A new technique for wheal production, based on immunological principles, is herewith presented. After passive sensitization of the

normal skin by the injection of serum from a hypersensitive patient, the wheal is produced at the site of injection by feeding the specific offending food.

3. The reaction is of internal origin, and results in a wheal which, to all appearances, simulates that of a constitutional urticaria.

4. Other advantages of this method of wheal production over those previously employed are presented and discussed.

For assistance in obtaining much of the above information, the writers are indebted to their colleagues, M. Brunner, H. Sussman, S. J. Wilson and S. Kramer.

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REVIEWS.

GOITER AND OTHER DISEASES OF THE THYROID GLAND. By ARNOLD S. JACKSON, M.D., of the Jackson Clinic, Madison, Wis. Pp. 300; 152 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, \$10.00.

THE author of this book, a devout follower of the Mayo Clinic School, has presented a treatise on the subject of diseases of the thyroid gland for the practising physician and particularly for the surgeon, based upon experience gained in the treatment of a large series of cases. The book is written almost in the semiconversational style of a surgical clinic, and is characterized by straightforward statements on diagnosis and treatment, in which indications for and against the use of iodine figure quite prominently. A simple working classification of diseases of the thyroid is presented in which the relatively new concept of "iodine hyperthyroidism" is given an important place.

Although it is primarily intended to be a practical treatise on diagnosis and treatment, one wonders whether in attempting to attain this difficult ideal the author has not been a trifle too didactic. Another criticism which might be raised is the relatively small space allotted to some of the important aspects of the normal gland. For instance, that very slightly over a single page should be allotted (in a work of about 300 pages) to the subject of the normal histology of the gland, seems a trifle scant; if we bear in mind the warning which Virchow expressed many years ago, and which indeed has been well borne out, that in order to gain a true conception of the structure of pathological lesions of the thyroid, the extreme lability of structure of the normal gland should be emphasized.

The book is, however, an important and useful publication and will undoubtedly fulfil the purpose for which it was written.

J. P.

SURGICAL ANATOMY OF THE HUMAN BODY. VOL. I. By JOHN B. DEEVER, M.D., Sc.D., LL.D., F.A.C.S. Second edition. Three volumes. Pp. 551; 124 illustrations. Philadelphia, P. Blakiston's Son & Co., 1926. Price \$12.00 each volume.

THIS, the second edition of *Surgical Anatomy* should warrant as great a reception as was given the first. The character of the

subject matter is such as to demand accuracy in description and detail, which accuracy is easily checked up by comparison with the standard works on anatomy. In this respect the book is beyond reproach. The illustrations are excellent, beautifully finished and serve as accurate reproductions. The fact that they are relief in character adds much to their value. The work is well edited, and the diction does much to relieve the reader from stereotyped style so commonly seen in books of this sort.

The author very properly in his preface gives unstinted praise to those who helped in the production of this work, a credit to all concerned.

The volume is attractively prepared with a splendid quality of paper and a good binding.

E. E.

MODERN METHODS OF FEEDING IN INFANCY AND CHILDHOOD. By DONALD PATERSON, B.A., M.B. (EDIN.), M.C.R.P. (LOND.), Physician to Out-patient Department, Hospital for Sick Children, and Physician to the Infants' Hospital, Westminster; and J. FOREST SMITH, M.C.R.P. (LOND.), First Assistant to the Clinical Unit, St. Thomas' Hospital, and late John and Temple Fellow in Diseases of Children, St. Thomas' Hospital. Pp. 106; tables in text. New York: Paul B. Hoeber, Inc., 1926.

THIS is a monograph on infant feeding adapted for ready use by the general practitioner. Breast feeding is admirably considered, in its normal management and in the surmounting of the difficulties which arise in many cases. Artificial feeding is discussed according to accepted present-day ideas. The authors give more attention to prepared milks and proprietary foods than do most American writers. The use of special formulas, such as lactic acid milk, protein milk, thick cereal mixtures and butter-flour soups deserves more detailed discussion.

J. S.

THE DIABETIC LIFE: ITS CONTROL BY DIET AND INSULIN. By R. D. LAWRENCE, M.A., M.D., Chemical Pathologist and Lecturer in Chemical Pathology, King's College Hospital. Second edition. Pp. 167; 11 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, \$2.50.

OF the various small diabetic manuals intended for both doctor and patient which have appeared in the last few years, this little volume is the best that has come to our attention. There is much in it that may be difficult for the patient to grasp at the first reading,

but the practitioner will find it all the more valuable. The only objection that occurs to a conservative is that the ration unit used in the working diet is rather high in fat, having a ketogenic-anti-ketogenic ratio of 1.62, as opposed to 1.5 top limit, as advised by Woodyatt. The popularity of the book is attested by the call for a second edition within a year of the first. R. K.

BRAIN AND HEART.—By GIULIO FANO, of the Royal University of Rome; translated by HELEN INGLEBY. Pp. 142; 19 illustrations. New York: Oxford University Press, American Branch, 1926.

Brain and Heart, a small volume, is a collection of lectures which were given before students who desired to learn of the author's investigations and scientific views. Because of this request, the style is almost autobiographical and is charmingly so.

The subject matter is concerned with discussions of "living matter," "some relations between inhibition and will" and "excitability and automatism." Interspersed among statements of scientific views, or of experimental data, are remarks so characteristic that one gains a conception of personality, a scientist, an artist, a man of letters. The translator has succeeded remarkably well in maintaining this personality as well as translating the facts, none of which are essentially new. J. S.

PATHOLOGY AND TREATMENT OF THE INFLAMMATORY DISEASES OF THE NASAL ACCESSORY SINUSES. By DR. M. HAJEK, of the University of Vienna. Translated by DR. JOSEPH D. HEITER and DR. FRENCH K. HANSEL. Fifth edition; first English translation; two volumes. Pp. 701, 186 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, \$17.00.

It is strange that this piece of work should have passed through four editions before being translated into English. The author, who was one of the pioneers in the field of sinus conditions, is the head of a Vienna clinic of world-wide reputation. Practically all English works on the subject have been greatly influenced by the observations of this clinic.

The present work of two volumes contains nothing new to the student of accessory sinus conditions, but covers the anatomy, pathology and surgery of these regions in detail. The anatomic studies which are so important to the rhinologist are especially good and are accompanied by an adequate number of illustrations. From the standpoint of pathology, the symptom complexes of the diseased

sinus conditions are well presented, as well as the gross morbid anatomy. The reports on microscopic studies of pathologic tissues are, however, rather meager, a feature which this work has in common with most other books on this subject. All the surgical procedures used today in the treatment of diseased sinuses are mentioned and their relative values stated. The large surgical experience of the author makes this portion of the book especially worth while.

K. H.

A PRACTICE OF PHYSIOTHERAPY. By C. M. SAMPSON, M.D. Pp. 620; 146 illustrations. St. Louis: The C. V. Mosby Company, 1926. Price, \$10.00.

THIS book is based on the author's previous work, *Physiotherapy Technic*, and is, like it, a very valuable contribution to the literature on physiotherapy. In addition to an excellent description of the physics and technic of the various applications, there is in this new volume much valuable information as to their use in a vast number of individual pathological conditions. The nature of the case and the aim of the treatment are constantly kept in mind. Description of apparatus and useful advice as to its proper care is also given.

The chapters on high frequency and actinotherapy are particularly well written, while altogether too small a space is devoted to those on massage and hydrotherapy to make them of much instructive value.

J. N.

PRINCIPLES OF DIAGNOSIS AND TREATMENT IN HEART AFFECTIONS. By SIR JAMES MACKENZIE, M.D., F.R.S., F.R.C.P., LL.D., Director of St. Andrews Institute for Clinical Research; Consulting Physician to the London Hospital, and JAMES ORR, M.B., CH.B., Physician to the St. Andrews Institute for Clinical Research. Third edition. New York: Oxford University Press, American Branch, 1926. Price, \$3.50.

INTENDED originally as postgraduate lectures, the contents of this book were changed through war exigencies into a statement of recent advances in cardiology for the general practitioner. The author's increasing insistence on the proper study of function and his development of the clinical applications of the principle of the reflex arc receive sympathetic attention in Dr. Orr's revision. The four parts of the book (heart failure, disorders of mechanism, other heart affections and prognosis and treatment) summarize the teaching of the longer book, *Diseases of the Heart* (*vide* AM. J. MED. SCI., 1926, 171, 593).

E. K.

BOOKS RECEIVED.

- Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1926.* Pp. 330. Washington: Government Printing Office, 1926.
- Report on Third International Congress of Military Medicine and Pharmacy, Paris, April 1925.* By WILLIAM SEAMAN BAINBRIDGE, Commander Med. Corps, U.S.N.R.F. Pp. 111; 28 illustrations. Reprinted from the Military Surgeon, May to August, 1926.
- Local Immunization. Specific Dressings.* By A. BESREDKA. Translated by HARRY PLOTZ, M.D. Pp. 181. Baltimore: Williams & Wilkins Co., 1926. Price, \$3.50.
- History Taking and Recording.* By JAMES A. CORSCADEN, M.D. Pp. 78. New York: Paul B. Hoeber, Inc., 1926. Price, \$1.50.
- Diseases of Women.* By HARRY STURGEON CROSSEN, M.D., F.A.C.S. Sixth edition. Pp. 1105; 934 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, \$11.00.
- Atlas of the History of Medicine. I. Anatomy.* By J. G. DE LINT. Pp. 96; 199 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, \$6.00.
- Transfusion of Blood.* By HENRY M. FEINBLATT, M.D. Pp. 137; 24 illustrations. New York: The Macmillan Company, 1926.
- Shell Shock and Its Aftermath.* By NORMAN FENTON, Ph.D. Pp. 173; 12 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, \$3.00.
- An Introduction to the Practice of Preventive Medicine.* By J. G. FITZGERALD, M.D., LL.D., F.R.S.C. Pp. 792; 130 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, \$7.50.
- Die Menschenthymus. I. Das Normale Organ.* By J. AUG. HAMMAR. Pp. 562; 352 illustrations. Leipzig: Akademische Verlagsgesellschaft M.B.H., 1926.
- Juckende Hautleiden.* By DR. S. JESSNER. Pp. 140; 1 illustration. Leipzig: Curt Kabitzsch, 1926.
- Neue Beiträge zur Morphologie und Physiologie der Cholesterinsteatose.* By DR. R. KAWAMURA. Pp. 267. Jena: Gustav Fischer, 1927. A valuable exposition of the occurrence of cholesterol esters in the animal body, based on a wide knowledge of the literature, as well as protracted individual research.
- Practical Surgery of the Joseph Price Hospital.* By JAMES WILLIAM KENNEDY, M.D., F.A.C.S. Pp. 361; 129 illustrations. Philadelphia: F. A. Davis, Company, 1926. Price, \$10.00.

- Physiology and Biochemistry in Modern Medicine.* By J. J. R. MACLEOD, M.B., LL.D. (ABERD.), D.Sc. (TOR.). Fifth edition. Pp. 1054; 291 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, \$11.00.
- Clinical Application of Sunlight and Artificial Radiation.* By EDGAR MAYER, M.D. Pp. 468; 70 illustrations. Baltimore: Williams & Wilkins Co., 1926. Price, \$10.00.
- Sketch of the History of the Mayo Clinic and the Mayo Foundation.* Pp. 185; 17 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, \$3.50.
- Medical Clinics of North America.* Mayo Clinic Number, November, 1926. Pp. 275; 55 illustrations. Philadelphia: W. B. Saunders Company, 1926.
- A Sound Economic Basis for Schools of Nursing.* By MARY ADELAIDE NUTTING, R.N., M.A. Pp. 372. New York: G. P. Putnam's Sons, 1926. Price, \$2.50.
- A Statistical Survey of Three Thousand Autopsies.* By WILLIAM OPHÜLS, M.D. Pp. 370. Stanford University, California: Stanford University Press, 1926.
- Pneumoconiosis (Silicosis) A Roentgenological Study.* By HENRY K. PANCOAST, M.D. and EUGENE P. PENDERGRASS, M.D. Pp. 186; 23 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, \$4.00.
- On the Skull and Portraits of George Buchanan.* By KARL PEARSON, F.R.S. Pp. 28; 11 illustrations. London: Oliver and Boyd, 1926. Price, Sixpence.
- The Normal Child and How to Keep it Normal in Mind and Morals.* By B. SACHS, M.D. Pp. 111. New York: Paul B. Hoeber, Inc., 1926. Price, \$1.50.
- Principles and Practice of Oral Surgery by Silverman.* Pp. 326; 280 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, \$6.00.
- Practice of Medicine.* By A. A. STEVENS, M.D. Second edition. Pp. 1174; 35 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, \$7.50.
- Ultra-Violet Rays in General Practice.* By W. ANNANDALE TROUP, M.C., M.B., C.H.B. (St. ANDREW'S). Pp. 59; 12 illustrations. London: H. K. Lewis & Co., 1926.
- The Principles and Scope of Homœopathy.* By JAMES W. WARD, M.D., F.A.C.S. Pp. 73. San Francisco: James W. Ward, M.D., University of California.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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An Experimental Study of the Synovial Fluid of Patients with Arthritis and Syphilis.—It is extremely difficult in the syphilitic to determine if an arthritis is the result of a syphilitic process or whether it is due to some other factor. CHESNEY, KEMP and BAETJER (*J. Clin. Invest.*, 1926, 3, 131) undertook to ascertain if there were any characteristic changes of the joint fluid or any characteristic roentgenologic manifestations which would aid in the diagnosis of these lesions and, lastly, they endeavored to recover the specific organism, *Spirochæta pallida*, from the synovial fluid. They conclude that in its response to treatment the arthritis was syphilitic in origin in 5 cases. From the synovial fluid of 3 of these 5 patients strains of *Spirochæta pallida* which were virulent for rabbits were obtained by inoculation of animals of that species. In 4 of the 5 patients with syphilitic arthritis the fluid from the joint showed a relatively high percentage of lymphocytes and mononuclear cells combined. No significant roentgenologic changes were noted.

Angina Agranulocytotica.—ROCH and MOZER (*Presse méd.*, 1926, 74, 1171) discuss the interesting condition which has recently been described by Schulz and about which but little has appeared in American literature. The condition of agranulocytotic angina most often occurs in women of middle age and is characterized by sudden onset, a grave infectious state, marked angina, frequently so severe as to be mistaken for diphtheria, and the all-important examination of blood which shows a considerable and marked diminution in the number of white blood cells, more especially of the granular, or polymorphonuclear cells. The lymphocytes and the monocytes in general are but little affected by this condition. The same statement applies to the red blood cells. The blood platelets also remain normal. In discussing the differential diagnosis the authors dismiss the possibility of mistaking the condition for almost any other condition associated with the same clinical syn-

drome by stating that septicemia, benzol poisoning, the leukemias and other similar conditions are not accompanied by such a pronounced fall in the white blood cells. Somewhat more difficult may be the diagnosis of arrested acute leukemia in the aleukemic phase and aplastic anemia. It is of interest to note the variety of changes in the blood pictures which occur with septic conditions of the mouth.

A Study of Sprue and Addisonian Anemia.—NEWHAM, MORRIS and MANSON-BAHR (*Lancet*, 1926, 211, 269) present as a clinical study 90 cases of sprue which have been treated in the Hospital for Tropical Diseases, London, in the five-year period, beginning in 1920. The subject is presented from two points of view, from that of the clinician and that of the hematologist, and the subjective and objective symptoms of this condition are contrasted with those of pernicious anemia in the first part of the paper, while in the second portion the blood changes receive the same consideration. It is in the latter part of the paper that the newest material is presented. An extremely careful study of the blood in 12 cases of sprue is recorded, including hemoglobin estimations, count of the red cells and the white cells, estimation of the number of nucleated red cells, and the morphology of the erythrocytes. In addition to these usual studies, they have made Price-Jones curves of the red cells, studied the cholesterol content of the blood, studied the blood grouping in different cases and applied the van den Bergh reaction to the blood serum. The usual blood counts show that it is very hard indeed to make a differential diagnosis of these two conditions by the hematologist. A study of the red blood cell size and of the Price-Jones curves shows the close resemblance to those seen in pernicious anemia, with the exception that there is not such a marked variation in the size of the erythrocytes in the former as there is in the latter condition. The cholesterol content of the blood in both conditions shows that there is nothing to be gained from the viewpoint of differential diagnosis, as both of the two conditions show that there is a hypocholesterolemia. The anemia of sprue follows closely the behavior of pernicious anemia blood as applied to the van den Bergh reaction. The authors conclude that the two conditions are produced by two different and definitely opposite etiologic agents; that the anemia which accompanies the two diseases is almost identical but that the symptoms and physical signs vary considerably. They state dogmatically that the anemia does not indicate a similar or even allied etiology, despite the almost identical blood picture nor do they show by a statistical study that there is any very marked difference in the symptoms of the two conditions. The only definite evidence that they give that the two lesions are dissimilar is in the statement that of the 90 cases, all the patients had been in the tropics, although they add parenthetically that in 10 patients the disease had not developed until the return of the individual to Great Britain. In this country it is considered now that sprue is not essentially a disease of the tropics, but may occur in subtropical and temperate climates, so that their positive statement that all these cases occurred in the tropics and did not occur in England probably would have very much less weight in this country as proof of the duality of pernicious anemia and sprue than would be attached to such a statement in England.

SURGERY

UNDER THE CHARGE OF

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Arthroplasty of the Hip.—BAER (*J. Bone and Joint Surg.*, 1926, 8, 769) writes that arthroplasty for the production of motion in certain joints and under certain conditions has taken its place in surgery as a definite procedure. Arthroplasty for ankylosis of the jaw is an operative procedure as permanent and exact as is the operation of appendectomy. Next to the jaw, arthroplasty of the hip has made the greatest strides and is well on its way of taking its place as a recognized surgical procedure. The author feels that arthroplasty of the hip for gonorrheal arthritis is not only a proper procedure, but it almost assures the patient of good motion in the hip. He would not hesitate to recommend such procedure to any patient applying for relief. The results of arthroplasty in traumatic ankylosis of the hip are very gratifying. Prognosis in septic infection of the hip should be far more guarded. It is difficult to tell what changes have been made in the human body by the previous continuous suppuration. Here one is dealing with latent fire. In tuberculous arthritis caution should be the motto. Opinion is generally against an arthroplasty. In some adults, apparently cured, but with exacerbation of fluid in the joint and its consequent disability, good results may be obtained. In arthritis deformans the procedure should not be used.

Giant-cell Tumor of Bone.—GORFORTH (*Arch. Surg.*, 1926, 13, 846) says that the known behavior of the giant-cell tumor warrants its being classified as a true neoplasm. The giant-cell tumors constitute a series. Those at the lower end of the scale possess relatively adult fibrous stromas and are essentially benign. Recurrences are more aggressive or virulent than the primary growth both clinically and microscopically. They are potentially malignant and may as a result of repeated or improper treatment undergo malignant transformation and metastasize. The giant cells or osteoclasts that are characteristically present function as bone absorbers and are of osteoblastic origin. They are not reliable indexes of the neoplasm's relative malignancy. The stroma is of fibroblastic origin, and its behavior governs the course of the giant-cell tumor. Through microscopic study of its cellularity, cell type and cell activity offers a fairly reliable criterion of the innocence or relative malignancy of the growth. History, thorough clinical and Roentgen ray study, and a rigid follow-up, are all necessary in establishing the final correct diagnosis and the true nature and behavior of the giant-cell tumor.

The Mortality Rate in Appendicitis—Is it on the Increase?—MARSH (*Boston Med. and Surg. J.*, 1926, 195, 1059) states that reference to the leading surgical clinics in this country reveals the fact that the mortality of major operative conditions is decreasing, while in the hands of the average surgeon the mortality, with the exception of pelvic conditions, shows a decided increase. However, the evidence of increased mortality rate as given out by the Bureau of Vital Statistics may be misleading and an apparent increase may be explained in other ways. Statistics from some of the hospitals of New England rather indicate that in that part of the country the rate is decreasing. It is from the advanced case that the mortality comes. There may be a surgical accident in any case or postoperative adhesions may cause mechanical ileus. There is the occasional wrong diagnosis and the frequently delayed diagnosis. Indifference to or ignorance of the significance of abdominal pain on the part of the patient, causing delay, is the greatest factor in raising the rate. To a less degree the procrastination of the doctor enters into it, and even less than either is the skill of the operator.

Bursitis of the Plantar Surface of the Foot.—HERTZLER (*Am. J. Surg.*, 1926, 1, 117) claims that the association of gonorrhea with exostoses and painful affection of the feet has not been proven. The association of pain in the feet with stretching of ligaments rests on the assumption of sensitiveness of ligaments. This conclusion was arrived at by a process of exclusion and is contrary to the facts. Certain painful affections of the feet occur in regions where bursæ are known to exist. The clinical manifestations are similar to those of bursal inflammations in other parts of the body. Obliteration of these bursæ by operation cures the patient. Operations based on other hypotheses (that is, exostosis) do not cure the patient unless the bursæ are inadvertently obliterated.

Diffuse Gastric Polyposis.—BRUNN and PEARL (*Surg., Gynec. and Obst.*, 1926, 43, 599) say that diffuse gastric polyposis is seemingly a rare disease, since the authors have only been able to collect 84 cases from the literature. They do not feel, however, that these figures represent the true incidence of the disease. The condition may be either congenital in origin or arise from an inflammatory basis. It is of interest that these tumors have been reproduced experimentally. The symptoms and physical signs are not characteristic. Achylia is the most significant finding. Combined with fresh blood and abundant mucus it should suggest the diagnosis. Malignant degeneration occurred in 12 per cent of the 84 cases collected. The treatment should be surgical. It is of interest that in our own and in the collected series no case of pernicious anemia has developed in spite of continued achlorhydria. In the authors' series 1 case lasted twenty-five years.

THERAPEUTICS

UNDER THE CHARGE OF

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Treatment of Postencephalitic Parkinsonianism of Nicotin.—MOLL (*Brit. Med. J.*, 1926, 1, 1079) reports 13 cases of postencephalitic Parkinsonian disease in which he used hypodermic injections of the pure alkaloid of nicotin to counteract the increased muscle tone and consequent apparent stiffness of joints. It was thought that, since the sialorrhea, rise in pulse rate and retraction of eyelids were signs of increased sympathetic stimulation, possibly the muscle tonicity was at least in part due to this same cause. McAlpine has described degenerative changes in the substantia nigra in the midbrain and in the anterior part of the globus pallidus of the lenticular nucleus. These lesions were thought to possibly interfere with the normal prespinal reflex arc and thus result in an increased plastic tone of the muscles. Nicotin paralyzes the preganglionic sympathetic cells, and thus might block the sympathetic prespinal arc. The treatment was initiated with doses of $\frac{1}{30}$ gr., three times a day. This was usually followed by a fall in pulse rate, then a rise with a return to normal in seven to ten minutes. The blood pressure also showed a gradual rise with a return to normal in about the same time. Other phenomena observed were flushing of the face, profuse sweating, tremors, thirst, nausea, vomiting and tachypnea. In 2 cases a fit with tonic spasm and loss of sphincter control followed by vomiting was noted. This initial dosage was kept up for a few days, until no untoward symptoms occurred, then it was gradually increased to $\frac{1}{10}$ or $\frac{1}{5}$ gr., three times a day, and continued for two to three weeks or until signs of intolerance appeared. Nine of the 13 cases were helped by this treatment, stating that "their joints felt looser." Of the other 4, 1 was a true Parkinsonian and was not helped and the other 3 seemed to derive no benefit at all. The action was only temporary, after six months time all the patients being just as badly off as before. The author concludes that nicotin is of temporary aid due to paralyzing the prespinal reflex arc subserving plastic tone and that the injections should be repeated every two to three months. The other symptoms, such as sialorrhea and tremors, were influenced in no way at all.

The Treatment of Intestinal Hemorrhage.—Also in *Monde médical* (October 1, 1926) there is an abstract of an article by TURPIN from *Progrès médical* on the treatment of intestinal hemorrhage: (1) In slight hemorrhage, rest, champagne and iced milk; subcutaneous injection of the posterior lobe of hypophysis or of 1 cc. of the following solution: Ergot, 2 gm.; glycerin and water, each 5 gm.; every half hour a teaspoonful of the following: Calcium chlorid, 4 gm.; syrup of opium, 30 gm.; water, 120 gm. (2) In severe hemorrhage, absolute

rest flat in bed; ice to the abdomen; nothing by mouth; subcutaneous abdominal injection of 500 cc. of artificial serum; every half hour a teaspoonful of the mixture mentioned above and two or three injections of posterior lobe of hypophysis in twenty-four hours. (3) In very severe hemorrhage with collapse and loss of consciousness, intravenous injection of 1 gm. of adrenalin, $\frac{1}{1000}$, in 300 gm. of water and 2 gm. of sodium chlorid. In cases where adrenalin is contraindicated he recommends the intravenous injection of 500 cc. of isotonic glucose associated with the subcutaneous injection of chloralhydrate of emetin. Also slow lavage with warm water containing 4 gm. of calcium chlorid, and again posterior lobe of hypophysis intravenously. In hemorrhages due to an alteration of the blood he uses subcutaneous whole blood, horse serum or transfusion.

The Intravenous Use of Hexamethyl Amine in Typhoid Fever.—In *Monde médical* (October 1, 1926) there is an abstract of an article by CHALIER and GRANDMAISON, published in *Progrès médical*, dealing with the intravenous use of hexamethyl amine (urotropin) in typhoid fever. These writers state that if the drug is injected just prior to or during the stage of bacteremia its bactericidal effect will tend to lessen the possibility of growth of organisms in the blood stream and their consequent spread to the various organs. As the urotropin is excreted in the bile and in the urine its use tends to reduce the complications of cholangitis and posttyphoid cholelithiasis and to lessen the number of urinary typhoid carriers. They have not seen a nephritis develop from its use, and think that albuminuria is no contraindication. In those cases where it has been used early in the disease the complication of intestinal hemorrhage seems to have been reduced.

PEDIATRICS

UNDER THE CHARGE OF

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The Effect of Various Supplementary Lunches on the Plasma Carbon Dioxid Capacity of Children.—MORGAN and HATFIELD (*Am. J. Dis. Child.*, 1926, 32, 655) made carbon dioxid capacity studies on 12 children upon whom they made other studies of nutrition. Five of these children were from 5 to 17 per cent underweight, according to the Baldwin and Wood Standard, 1 was 33 per cent overweight and 6 were practically normal in weight. The 6 normal children showed alkaline reserve figures of 42 to 65 per cent or cubic centimeters of carbon dioxid per 100 cc. of plasma. Four of the 5 underweight children showed corresponding values of 38 to 51. One child who was given figs as a supplementary lunch gained more than three times the expected

amount in weight, and showed an increase of 5.5 per cent in carbon dioxide combining power of plasma after a period of forty-three days. Five children who were given oranges as a supplementary lunch, and upon whom two or three alkaline reserve determinations were made at twenty-eight to fifty-day intervals showed increase in carbon dioxide combining power of plasma of 1.7 to 11.19 per cent. Those subjects who failed to make the expected gain in weight during these periods also showed the lowest gains in alkaline reserve. Two out of 3 children who were changed from oranges to milk after a twenty-eight day interval showed a decrease in alkaline reserve of plasma of from 3 to 7.78 per cent. The third child showed an increase of 1.37 per cent after a forty-three day interval on milk. Whether the alkaline reserve values observed were indicative of a cumulative relatively steady rate of change or were variable random figures modifiable within a few hours by a change in diet is a question which can be definitely answered only by day to day observations on a number of subjects.

Breast Feeding Problems.—MOORE and DENNIS (*J. Am. Med. Assn.*, 1926, 87, 1970) emphasize that to overcome the mental hazards of motherhood regarding breast feeding physicians must stress the fact that every mother who can care for her baby can nurse it. They also point out that daily health routine of the lactating mother needs more careful study and regulation by the physician. The amino acid and vitamin B content of the diet are very important. During this period a milk diet is very inadequate. Abnormal constitutional conditions, including contagious diseases in the mother may necessitate artificial feeding for a time, but the glands should be kept active by manual expression, so that the breast feeding may be restored at the earliest possible moment. Open tuberculosis in the minds of the authors is the only absolute indication for weaning. Premature weaning is at present too frequently the result of remediable conditions in the mammary glands. Breasts and nipples deserve a complete examination, including inspection, palpation and milk expression. Nipple muscle hypertrophy and hypertonicity are curable. Aseptic care of the nipples together with the use of nipple aerators prevents infections, fissures and mastitis. Aerators evaginate everted nipples and permit the necessary open air treatment. The cancer fear, as an excuse for avoiding nursing or manual expression is refuted by experience and by statistics. Manual expression is the best means of improving an insufficient maternal supply.

The Effects of Diet on Rickets.—GREENEBAUM, SELKIRK, OTIS and MITCHELL (*J. Am. Med. Assn.*, 1926, 87, 1973) report a study of the effects of actively regulating diets of pregnant women on the development of rickets in their offspring. These observations were made on 25 women who had previously had rachitic children, and the period of observation covered both winter and summer seasons. One mother whose infant did not develop rickets was 1 of 2 in whose diet throughout the last months of pregnancy there were approximated the standard sought. In the infant of this other mother rickets was not found until after the eighth month. The average daily caloric intake of the mothers whose infants developed moderate and marked rickets were as a group lower than in the group whose infants developed mild rickets. In the

entire series, regardless of the degree of rickets, the mineral intake of the mothers was approximately the same. In those cases in whom blood examinations were made the inorganic phosphorus content of the blood obtained in the antepartum period was uniformly normal, while the inorganic phosphorus content of the babies' blood was below normal. The calcium content of both mothers' and babies' blood was normal. A low calcium content of the breast milk was often found, and this possibly was the result of the inadequate diets of the mothers during the lactation period, since practically all of them returned during that time to the previous habits of eating, consuming a diet in which milk, especially, was lacking. The inorganic phosphorus of the breast milk was uniformly normal. The season of the year in which the babies was born apparently had no influence on the degree of rickets, although an absolute conclusion cannot be reached on account of the small number of cases in the series. Five of the babies found by Roentgen ray to have rickets had no clinical evidence of the disease. Two babies whose Roentgen ray studies were negative for rickets were considered to have rickets clinically. The incidence of rickets in this group of 22 babies to whom cod liver oil was not given was as follows: By the eighth month 16 showed rickets on clinical examination, or 73 per cent, and 19 showed rickets by Roentgen ray examination, or 87 per cent. As the result of this study, the authors feel that if the diet of the mother during the last three months of pregnancy can be made approximately correct in caloric and mineral intake, while it will not prevent rickets, it will have a controlling influence in the development of the disease in the child.

Scarlet Fever.—PLATOU and COLLINS (*Arch. Pediat.*, 1926, 43, 707) report that small doses of 3000 skin test doses of scarlet fever toxin detoxified with sodium ricinoleate did not protect 8 nurses who were exposed to the disease from three to seven weeks after receiving the injection. Among individuals that are kept Dick negative by inoculation or reinoculation with the same preparation in larger doses there were no cases of scarlet fever in spite of intimate exposure. Increasingly large initial doses of toxin may prevent the necessity of reinoculation in order to preserve immunity. The administration of a total of 9000 skin test units of Larson's detoxified preparation rendered a large percentage of children Dick negative for a period of a year. The commercial preparations of scarlet fever antitoxin used in a comparative study of 190 cases were apparently specific. Acceleration in clinical improvement as gauged by temperature, rash and symptoms was quite definite in 100 cases receiving the antitoxin. This was especially true in those to whom antitoxin was administered early. Better results might have been obtained if larger initial doses of antitoxin graded in units according to the blanching power per cubic centimeter could have been given. When given early the serum has a beneficial effect on the toxemia and seems also to reduce the number of complications, although no effect on septic processes was noticeable. The small prophylactic doses given to 5 cases in this group did not prevent later infection with scarlet fever. In one-fourth of the cases serum sickness was an annoying factor and in 11 cases it was extremely discomforting to the patient, especially in those who had been sensitized previously to horse serum through diphtheria immunization.

DERMATOLOGY AND SYPHILIS

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On the Urticarial Reaction and its Physiologic Meaning.—This is essentially a summary of the joint work of GRANT (*Brit. J. Dermatol. and Syph.*, 1926, 38, 425) with Sir Thomas Lewis on a recent interpretation of the physiologic meaning of the urticarial reaction. There is a type discrepancy between the dilution of histamin mentioned in Grant's article and the dilutions used by Sir Thomas Lewis in other reports, the former speaking of 1 in 30,000 and the latter of 1 in 3000. Lewis and the author believe that the urticarial reaction is a type of defense mechanism on the part of the skin which is uniform for every form of trauma, including mechanical injuries, such as stroke, prick and scratch; burning heat; cold and freezing; galvanic currents; ultra-violet light; chemical substances, including hydrochloric, lactic and formic acids, morphin, atropin, cantharidin and many other substances; antigens in subjects susceptible to the protein concerned. This urticarial reaction takes place upon the liberation of a theoretical histamin like substance in the "traumatized" skin. They base this belief upon the essentially identical character of the reactions produced by the stroke and by the pricking of histamin in a dilution of 1 to 3000 into the skin. In both cases a red line or red spot appears in about twenty seconds, which is best seen when the veins are slightly congested. In persons who exhibit a dermatographism a wheal appears along the stroke, and around the pin prick in the case of the histamin. If the venous pressure in the arm be raised sufficiently to close the arterial circulation no wheal appears, although the red spots develop, indicating that the latter is a vasoparetic phenomenon. The flush is arterial in origin and is controlled by the nervous system through a local nervous reflex, which persists even when the nerves to the skin are freshly divided, although it disappears when the cutaneous nerves have degenerated (not dependent on a spinal reflex arc). The wheal develops as a consequence of increased permeability of the vessel walls, as shown by Ebbecke, who found that trypan red injected into the circulation would not pass through the vessel walls unless an injury had taken place. The authors believe the increased permeability to be independent of the nervous system, because it will appear on anesthetized skin. The reactions of the histamin and the stroke wheal to changes in venous pressure, heat and cold are practically identical.

The third argument advanced by the authors for the identity of the histamin and other types of wheal formation is the establishment of *refractoriness*. If the appearance of the wheal is prevented by arresting the circulation for fifteen minutes or more no subsequent wheal formation can be obtained, even though more histamin be introduced into the previously pricked area. The failure of the wheal to appear and the failure of response to further stimulation, constituting refractoriness, occurs in all the forms of wheal excitation mentioned above. The authors believe that factitial urticaria is due to an exaggerated susceptibility of the cells of the skin, which respond to mechanical injury by release of a diffusible substance. The work of Hare and Lewis and a number of his coworkers is cited in support of these statements. This group of observations is of particular interest because it again brings into the field of causation of cutaneous inflammatory reactions the histamin hypothesis proposed by HARRIS in 1916 (*Arch. Dermatol. and Syph.*, 1921 3, 579). This author proposed on theoretical grounds that histamin acting as the antagonist of adrenalin was capable of explaining the clinical picture of eczema, including the vascular phenomenon and the itching inseparable from that condition. Thus far, of course, the influence of histamin is largely a matter of inference, inasmuch as no such substance has been identified in any of the local lesions involved. Its formation in other parts of the body, however, and its possible absorption into the blood may provide a basis for further investigation and verification of this significant hypothesis.

OBSTETRICS

UNDER THE CHARGE OF

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Retrodisplacement of the Uterus during Pregnancy and the Puerperium.—DANFORTH and GALLOWAY (*J. Am. Med. Assn.*, 1926, 87, 826) set forth the findings of a large number of cases during pregnancy and following labor. About 20 per cent were found to have retrodisplacements, and the authors consider that retrodisplacement as a pathologic entity has been overemphasized. They believe far too many operations are performed for the correction of the displaced uterus. In certain cases of sterility they believe displacement the causative factor. The operative treatment is not discussed. The

routine examination in the early months of pregnancy makes known the fact of the position and the movability of the uterus. If retro-displaced, it is left in this position, subsequent examinations determining whether it has risen out of the pelvis or whether it has been prevented in so doing by incarceration below the promontory. Manual replacement is ordinarily undertaken. The Schultz method is used if the manual reposition fails and a pessary is put in place suitable to hold the uterus in position until the growth of the uterus is assured; so that it cannot again become retrodisplaced into its old position. The displacement of the uterus provides an intelligent observation, being carried out during pregnancy. A large proportion of the retro-displaced uteri correct themselves spontaneously. The large majority can be manually replaced without anesthetic and held in position by mechanical measures. About 14 per cent of the retrodisplacements of uterus during pregnancy become retrodisplaced in the puerperium.

Etiology and Diagnosis of Intrauterine Fetal Death.—BROWNE and KINCAID (*J. Am. Med. Assn.*, 1926, 87, 847) report on experimental work on a case and brings out a probable cause of intrauterine fetal death during pregnancy. Those cases which have formerly been classified as idiopathic can, in all probability when fetal syphilis, fetal anomalies, toxemias of pregnancy and acute maternal infections are ruled out, be laid to direct infections of the fetus itself. The case reports and case experimental studies are given in detail. The article suggests that in a clinically healthy mother a fetus may apparently succumb in *utero* to a hematogenous streptococcal infection.

Trial Labor in the Treatment of 477 Cases of Contracted Pelvis.—BAILEY (*Am. J. Obst. and Gynec.*, 1926, 12, 550) deals with a large number of cases covering a period of four years and conducted under one plan of treatment. It covers the mortality of Cesarean section in a number of states of the mothers and infants following a careful canvass and the results of a questionnaire in the trial labor; all pelvises with the true conjugate below 7 cm. are called absolutely contracted, and should be delivered by elective section. All other patients of this series with relatively contracted pelvises, with the exception of those who were previously Cesareanized were given trial labor. The trial labor consisted in allowing the patients to have twelve hours of strong pains without rectal or vaginal examination. If at the end of this time the head was floating, a low section was performed; if the head was in the pelvis the patient was delivered by permitting the labor to continue and using forceps. The article classifies the pelvic contractions of the pelvis into minor and major, according to the diameter of the true conjugate. The funnel pelvis and irregular contractions are also tabulated. As an end result the author sets forth the maternal death rate as 0.42 per cent and an infant death rate of 4.19 per cent. The author clearly shows in the series of cases that trial labor in relatively contracted pelvises reduces the incidence of operation and results in a minimum mortality for mother and child, provided that when a Cesarean section is necessary the low operation be performed.

GYNECOLOGY

UNDER THE CHARGE OF

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Treatment of Cancer of the Cervix.—In his survey at the University of California Hospital during the past ten years, LYNCH (*Surg. Clin. North America*, 1926, 6, 333) has treated nearly 400 pelvic cancers, and he has a fairly good follow up review on which to base his opinion of the results. His experience has demonstrated to him that the ordinary panhysterectomy with the removal of the adnexa is useless from the standpoint of cure, because the growth is insidious and has usually extended beyond the confines of the uterus when operation is attempted. The ordinary hysterectomy cannot be radical except in the rarest of cases, since the ureters so closely parallel the sides of the upper cervix, where the lymphatic circulation is most abundant. He has never seen a cure of squamous cell epithelioma of the cervix where the diagnosis was apparent to the naked eye. The few cures that he has seen from ordinary hysterectomy were limited to cases in which the disease was microscopic in character and presented no definite lesion to the eye. While he believes, like most other surgeons at the present time, that radium offers the best prospect of relief in most cases of cervical cancer, nevertheless in the early cases he still feels that the extended operation is the method of choice. He has done 49 radical operations, with a mortality of 8 per cent, this series including cases which were primarily operable and those which were inoperable when first seen but which were treated and made operable by radium. Of the 16 primary operable cases which have survived five years, there are 8, or 50 per cent, which apparently are cures. At the present time, therefore, he is of the opinion that all the truly operable cases that are good risks should be operated upon after preliminary radiation, while all the other cases should be treated by radium alone. In support of the radical operation, he states that those who survive the operation are far more likely to escape a cancer death than those treated by radium, while those who die from the operation are saved from the more hideous cancer death. He warns again attempting to operate upon any of the cases in the so-called borderline group.

Treatment of Sterility by Roentgen Ray Therapy.—In a recent contribution to the subject of sterility, to which subject he has previously contributed such important work, RUBIN (*Am. J. Obst. and Gynec.*, 1926, 12, 76) discusses his experience with the use of Roentgen ray therapy in the treatment of that type of sterility which is associated

with habitual amenorrhea. This therapy is based on the supposition that the Roentgen ray exercises an irritating effect upon unfunctioning ovaries when applied in small dosage, although it has also been considered that the irradiation causes a regressive change in a persisting corpus luteum which has been the factor in prolonging the amenorrhea. In a rather large experience Rubin has found that habitual amenorrhea is associated with sterility in about 5 per cent of cases. Pregnancy takes place in about 5.5 per cent of the untreated cases. In 9 out of 12 cases treated with mild doses of Roentgen ray pregnancy resulted (that is, 75 per cent of the treated cases). Only 1 of these patients aborted. The rest carried to full term and gave birth to normal children. Roentgen ray irradiation of the ovaries resulted in restoration of the menses in 11 out of 12 cases of amenorrhea. Roentgen ray irradiation of the hypophysis area and the thyroid appears to have an adjuvant value. Two of the pregnant cases and 2 of the non-pregnant cases received hypophyseal irradiation. One of the pregnant cases also received thyroid irradiation. Peruterine tubal insufflation and endocrine therapy are additional aids to the therapeutic action of the Roentgen rays in cases of amenorrhea associated with sterility. As the ovaries were found to be definitely enlarged before treatment in 8 of the 9 successful cases treated with Roentgen rays, careful examination with regard to this point may prove of aid in selecting the cases or amenorrhea associated with sterility suitable for ovarian stimulation. When no ovarian enlargement is found irradiation to the hypophyseal area or the thyroid, etc., may be more advisable, and should certainly precede irradiation of the ovaries.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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The Arterial Pressure in the Eye.—DUKE-ELDER (*J. Physiol.*, 1926, 62, 1) constructed an apparatus to measure directly by means of a manometer the pressure within the central artery of the retina and its branches. Five experiments on cats gave an average systolic pressure of 88.5 mm. of mercury; diastolic, 64 mm. of mercury. Mean pressure interpreted as $\frac{S + D}{2} = 76$ mm. of mercury in the ophthalmic artery.

The intraocular tension was 24 mm. of mercury. Taking the point of maximal pulsation as a diastolic and that of the cessation of pulsation as the systolic pressure, the result of a series of six experiments by an oscillatory method gave for the systolic pressure within the posterior ciliary arteries 115 mm. of mercury; diastolic, 78.5 mm. of mercury; $\frac{S + D}{2} = 97$ — mm. of mercury. Intraocular tension was 25 mm. of

mercury. The carotid pressure was 106 mm. of mercury. He assumes that in the ciliary body the arterial mean pressure is about 75 mm. of mercury, that the venous pressure is about 25 mm. of mercury, while the intraocular pressure is about 24 mm. There is thus a fall in the vascular system of about 50 mm. of mercury. In man he assumes that the pressure gradient from the arteries to veins is more than 50 mm. of mercury. When it is remembered that the intraocular pressure is 20 to 25 mm. of mercury it would seem that the arterial and venous pressures in the eye bear a relation to the chamber pressure similar to that which the vascular pressures do to the tissue pressure throughout the body generally. The tissue lymph contains about one-half the quantity of colloids that are found in the blood, while the aqueous is practically protein free. Consequently, if the fluids of the eye can be formed without the intervention of a "secretory" mechanism the capillary pressure in the eye must exceed the intraocular pressure by more than the difference that obtains generally between capillary and tissue pressure. In round figures, a difference of 30 mm. of mercury must exist in the eye instead of 15 mm. elsewhere. There is every indication that this may be so. In the first place, the ciliary arteries seem to be anatomically peculiar in that they break up almost at once into a rich network of capillaries which appear to be capable of rising to a considerable height. Again, the veins are physiologically constricted at their exits from the eye, and the whole system is confined under a considerable tension within a feebly distensible case, the sclerotic, which will make the vessels approximate in their behavior to a system of rigid tubes. These considerations will all tend to throw the site of the fall of pressure further toward the veins and make it probable that the pressure in the arterial capillaries rises at least 30 mm. of mercury higher than in the chamber of the eye, that is, to a total of about 50 to 55 mm. of mercury. The vascular pressures, therefore, although by themselves they prove nothing, make it possible that the aqueous humor is formed purely by a process of dialyzation.

Blastomycosis of the Cornea with a Review of Reported Cases of Blastomycosis of the Eye.—McKEE (*Int. Clin.*, 1926, 3, 50) was consulted by a man, aged forty-three years, because of involvement of the eyes in a blastomycotic infection of the face and neck which had been present for three years. While shaving he cut a small pimple on his left cheek. Within a week he noticed a small raised area about the size of a pin. This spread slowly at first, then quickly, involved the left lower eyelid, then went across the nose to the right lids, under the ear and under the chin. The right lids were completely involved in irregular papilla-like elevations from which pus oozed upon slight pressure. The lids on the left side were practically gone. Besides a large leukoma there was found on the cornea of the left eye an ulcerative process. Smears from the conjunctiva were negative, but those from the cornea showed typical blastomycosis. The corneal ulcer healed very quickly with ordinary measures. General condition improved promptly under the administration of potassium iodid.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Pathology of Deaf Mutism.—"In the first decade of our century, when this research became known, it was supposed that certain alterations were characteristic of deaf mutism, just because similar changes were found in the labyrinth of congenitally deaf animals, for example, the Japanese dancing mice, albino cats and dogs, etc. Later on, however, it was shown that analogous abnormalities may exist also in cases of simple deafness. This may exist also in cases of simple deafness. Furthermore, similar anomalies were described in experimental labyrinth pathology and to this discovery we owe much insight into the pathogenesis of inner-ear diseases. It may be added that in isolated cases histologic research did not result in finding any local changes. It is supposed, therefore, that there must exist anomalies of the central connections and the brain. The pathology of deaf mutism for this reason does not represent something that is entirely confined to the labyrinth of the deaf mute. In the same way the conception of deaf mutism, though accepted generally as a clinical term, scientifically is not correct because, according to Bezold's hearing tests, in fact only a small number of so-called deaf mutes are totally deaf; the latter belong mostly to the acquired forms of deafness." Limiting himself solely to deaf mutism and its local manifestations in the ear, NAGER (*Laryngoscope*, 1926, 36, 313) emphasizes the importance of the central lesions and their histologic changes. In acquired deaf mutism the results are, as a rule, those of inflammatory processes in the labyrinth, whether meningitic, tympanic or hematogenic in origin. Deaf mutism caused by meningitis has been known longest and best. In such cases a new formation of bone and connective tissue of varying degrees up to complete obliteration of the labyrinth cavities occurs. If the cochlear duct is preserved it will show important changes, such as collapse, dilatation or adhesions. Corti's organ is missing, as are the cells of the stria vascularis. The membrana tectoria is often enclosed in an epithelial capsule. The spiral ganglion and nerve fibers are absent. In lymphatic labyrinthitis very extensive destruction or complete obliteration of the labyrinth is found, not infrequently coupled with cholesteotoma. The pathology of congenital deaf mutism is much more many-sided. In the endemic congenital type one deals with one of the symptoms of endemicroretinic degeneration, where there is a marked hyperostosis of the promontory, with a narrowing of the window inches and adhesions of the deformed stapes. In the cochlea a small hyalin body embedded between the organ of Corti and the membrana tectoria is found. In sporadic deaf mutism the changes are exclusively in the labyrinth, usually bilateral. They

have been regarded as malformations, ranging from the rare absence, through the slighter change in the neuroepithelium of the scala media, to the sacculocochlear degenerations, which comprise 70 per cent of sporadic congenital deaf mutes with remnants of hearing and include most of the constitutional hereditary form. Here, again, different grades of development are observed—those with defective central axis and those with large dilations of the saccus endolymphaticus. Besides these forms very marked malformations of the cochlea may exist, as the presence of only 1.5 coils instead of the normal 2.5 coils. It is very interesting to observe that tuning-fork examination revealed defects even in the inferior tone limit in cases in which the upper cochlear coils were absent. In a considerable number of these cases the bony labyrinths showed distinct spots of otosclerosis.

The Early Signs of Cancer of the Esophagus.—According to GUISEZ (*Presse méd.*, 1926, 34, 964), dysphagia of solid food is an early and characteristic sign of esophageal cancer. On the other hand, fluids and soft food may be swallowed with ease, in contradistinction to the discomfort encountered when similar substances are ingested in spasm of the gullet. When the carcinoma occurs in the upper portion of the esophagus, a symmetrical white or black coating at the base of the tongue, lateral to the median raphe, is the rule. While blood-streaked sputum suggests an esophageal neoplasia, a single attack of hematemesis is often seen in esophagospasm. The diagnosis can be clarified by esophagoscopy and biopsy. The author states that radium is of value in the treatment of esophageal malignancy.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Imbibition of Dyes by the Aortic Wall.—Intravenous injections of colloid solutions of trypan blue and carmin, as well as lipoids, have been shown to form deposits on the aortic wall by several workers. OKUNEFF (*Virchow's Arch. f. path. Anat.*, 1926, 259, 685) thought he would be able to arrive at conclusions regarding the origin of arteriosclerotic changes by injecting 1 per cent solutions of trypan blue by various routes into different types of animals. He gave these injections subcutaneously, intraperitoneally, intravenously, into the stomach and into an intestinal loop, and also varied the length of time that the

animals were exposed to the dye. It was found that the flecking of the aortic wall and its localization occurred in rats, mice and rabbits, but was not so characteristically similar to the conditions found in the human as was that in cats and dogs. The areas of imbibition were found to give support to Virchow's view, that the stagnation of the blood plasma determines the site, namely, at the branchings of the innominate and subclavian arteries, at the ductus arteriosus, at the coronary sinuses, in the region of the semilunar valves and along the descending aorta at the orifices of the intercostals. The subcutaneous and intraperitoneal routes gave staining in two to three hours and gave a maximum response with the dye in contrast to the slow and poor-staining produced by the enteral injections. The intima showed the greatest amount of dye, but penetration into the elastic layer was also noted. The flecking found by using dyes was analogous to that found in cases of arteriosclerosis and also to localization of lipoids in children, as well as to the results after experimental injection of lipoids. The origin of the pathologic changes in the aorta seems to be from the chronic absorption of fat mixtures in the intestines, which are transported to the aorta through the blood stream. The sites of deposition are doubtless decided by mechanical factors as well as to the localization of the lymph circulation, that is, there is a heaping of the lipoids at the points of greatest diffusion of plasma from the bloodvessel into the lymph stream.

Hemochromatosis and Chronic Poisoning with Copper.—MALLORY (*Arch. Int. Med.*, 1926, 37, 336) has been making a study of cirrhosis of the liver, and in analyzing the cases occurring in the Boston City Hospital he finds they can be divided into five groups: Infective, biliary and syphilitic, toxic, alcoholic and the pigment cirrhosis. The latter has occupied his attention recently, inasmuch as experimental work with rabbits and monkeys has confirmed his opinion that chronic copper poisoning is the true etiology of hemochromatosis and bronzed diabetes. The same type of lesion was found in the animals as in the autopsy material. Furthermore, a study of the clinical side of the cases showed that nearly two-thirds of the group were exposed over long periods to copper either through alcohol made in copper worm stills or through their occupations. A considerable number of the group were shown to be exposed, through canned fruits or other foods and drinks. It would seem that evidence is steadily accumulating in favor of the view that chronic copper poisoning causes the symptom complex known as hemochromatosis, pigment cirrhosis or bronzed diabetes.

Primary Carcinoma of the Liver.—It would appear from the recent work of COUNSELLER and MCINDOE (*Arch. Int. Med.*, 1926, 37, 363) that primary carcinoma of the liver only occurs in about 0.08 per cent of all autopsies. They report 5 cases and find that 4 of these 5 appeared to rise from the liver cell itself while the other appeared to have arisen from the cells lining the finer bile canaliculi. Males predominated. The usual clinical diagnosis was cirrhosis of the liver, and it has now been shown that very rarely is primary carcinoma of the liver not preceded by cirrhosis, which probably forms one of the predisposing factors to the malignancy. The gross appearance of these two types

of liver carcinomata varies, being massive, nodular and diffuse. No apparent relation exists between the gross and microscopic pictures, though the massive form is usually derived from the liver cells. Metastases occur in both types, but are usually intrahepatic, that is, into the portal and hepatic veins. It would appear that the origin of these growths is unicentric, as no transitional forms were found. All the cases were associated with cirrhosis of the portal type. Probably 3 to 4 per cent of such cases of cirrhosis result in carcinomata.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Further Studies on a Diplococcus from Measles; Prevention of Measles by Immune Goat Serum.—TUNNICLIFF and HOYNE (*J. Inf. Dis.*, 1926, 38, 48) state that the serum of a goat convalescing from a resection produced by the inoculation of green-producing measles diplococci protected rabbits against a subsequent injection of infective material from measles. The rabbits injected with normal goat serum and those untreated showed some or all of the characteristics of measles in rabbits—a rise of temperature, Koplik spots and an eruption. Convalescent goat serum protected human beings against measles as effectively as convalescent human measles serum when injected on the first and second days after exposure to measles. By intracutaneous tests in normal rabbits the serum of goats injected with diplococci from measles, as well as convalescent human measles serum, were shown to neutralize the action of killed measles diplococci, while serum of normal goats had no such effect. The serum of one immune goat was found toxic to nearly all persons injected with it, but after eight months preservation it appears to have lost its toxic effect. While these experiments do not furnish conclusive evidence of the protective value of immune goat serum, they warrant further investigation.

Some Nutrition Experiments with Brewers' Yeast.—SMITH and HENDRICK (*Pub. Health Repts.*, 1926, 41, 201) present the following conclusions, after giving details of the experiments leading to these conclusions: Dried brewers' yeast contains some factor essential in nutrition other than vitamin B. This factor withstands autoclaving

at 15 pounds' pressure for six hours. It is not in the heat and acid coagulable yeast protein. It is capable of adequately supplementing a ration in which the oat kernel is the sole source of protein and vitamin B. Evidence is advanced to show that a synthetic ration with casein as the sole source of protein must be supplemented with this unrecognized factor present in yeast, besides vitamin B, in order to make it adequate. When properly supplemented, oat protein appears to be just as satisfactory in the nutrition of the rat as is casein protein.

Four Cases of Tularemia (Three Fatal) with Conjunctivitis.—FREESE, LAKE and FRANCIS (*Pub. Health Repts.*, 1926, 41, 369) report an outbreak of tularemia due to the eating of undercooked rabbit by a family living in southwestern Virginia. The fatality rate was extraordinarily high—3 of the 4 cases dying. The onset was sudden, with fever, headache, vomiting, chills and in 1 case convulsions. Soon the temperature rose to 103° to 104° F., and there developed conjunctivitis, with swelling in the region of the parotid, bilateral in all but 1 case; later cervical and axillary glands became swollen and the picture was one of extreme febrile intoxication. A culture of the causative organism was secured from nasal swabbings after passage through a guinea pig, and the blood serum from the case which recovered gave agglutination with *Bacterium tularense*. The 3 fatal cases had been buried before the nature of the disease was suspected. An experiment on a rabbit dead of tularemia showed that in spite of apparently satisfactory cooking the infection might remain in the deeper parts.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 20, 1926

The Selective Absorption of Normal Goat Serum.—J. D. ARONSON (from the Laboratory of the Henry Phipps Institute of the University of Pennsylvania). Fresh normal goat serum produces necrosis when injected into the dermis or into the subcutaneous tissue of normal guinea pigs. When injected directly into the general circulation or into the peritoneal cavity death results. Furthermore, the addition of fresh normal goat serum to washed guinea pig cells hemolyzes these cells. It seemed likely that these differences in the results obtained from injecting the serum into different parts might depend upon the fixation of the serum by the different tissues. Experiments were undertaken to determine whether there existed a selective absorption by the different tissues for the hemolysin, necrotizing substance and toxic substance of normal goat serum.

The organs of normal guinea pigs were ground in a mortar with salt

solution, filtered through gauze and washed. To varying amounts of the washed tissue cells 2 cc. of fresh unheated goat serum were added, and the mixture of cells and serum shaken for two hours at 37° C. After centrifugalizing, the supernatant serum was collected and tested for its hemolytic action on guinea pig cells and for its necrotizing and toxic action on guinea pigs.

It was found that while the adrenal, heart, voluntary muscle and spleen did not absorb the hemolytic or necrotizing substance, the liver, kidney, skin, testes and erythrocyte stroma absorbed the hemolysin and necrotizing substance. The brain and lungs showed some absorption of the hemolysin and absorbed completely the necrotizing substance. The toxic substance was absorbed by suspensions of kidney, liver and testes, but not by the spleen.

When suspension of the different guinea pig tissues were heated at 70° C. or higher for thirty minutes, or were heated at 100° C. for ten minutes, their ability to absorb the goat serum hemolysin and necrotizing substance was decreased or destroyed completely.

It was found that erythrocytes of rats and mice were relatively resistant to the hemolytic action of normal goat serum, and that these animals were insusceptible to the necrotizing and toxic action of normal goat serum. Suspensions of the spleen, brain, liver, kidneys and testes of rats prepared in the same manner as those from guinea pigs were unable to absorb the hemolysin present in normal goat serum.

The fixation of the hemolysin to the kidney or liver cells is a firm one, and the hemolysin could not be dissociated from the cell by extracting with salt solution, distilled water, 0.1 per cent sodium carbonate or by freezing and thawing.

Studies of Gastric Acidity in Infants.—J. STOKES, JR., and J. TATUM (from the Department of Pediatrics of the Medical School of the University of Pennsylvania). The present studies of gastric acidity followed a comparison of the electrometric and colorimetric methods for determination of the pH of gastric contents (*J. Biol. Chem.*, 1926, 69, 75) and studies of the alteration in pH of the gastric contents after passage of the stomach tube in subjects with gastrostomies (*Am. J. Dis. Child.*, 1926, 32, 667). The object of the present studies was to examine by the electrometric method the pH of gastric contents obtained with as little gagging or contamination with saliva and mucus as was possible. Attempts to make normal infants regurgitate their meals with slight stimulation of the gagging reflex were usually unsuccessful. Certain specimens of gastric contents were obtained readily by gagging, but the great majority were obtained by passage of a catheter through the nose, assisted by pressure on the abdomen, the entire process consuming a relatively short period. By this method, in which the quantity of gastric contents compared favorably with the amounts obtained by other methods, it was felt that the alkaline diluents, which usually contaminate the gastric contents obtained by the ordinary use of stomach tube with the suction of a syringe, were practically eliminated, and that more accurate values for the pH of the gastric contents were found.

The pH of the gastric contents of newborn infants before the administration of milk or water averaged 1.6, the lowest value found being pH 1.026.

In normal infants under ten days of age the average pH of the gastric contents obtained one to one and a half hours after breast feedings was 2.9. This figure would have been low, except for 3 or 4 subjects whose gastric contents showed consistently a pH of about 5.0.

In normal infants of ten days to six months of age the average pH of gastric contents obtained in this way was 3.9.

An infant suffering from lobar pneumonia was found to be an interesting subject for study, since the slightest stimulation of his gagging reflex would evacuate apparently his entire gastric contents. His gastric contents were examined from the second day of his illness to the sixth day of his convalescence. Increased acidity of the gastric contents followed definite lowering of the temperature early in the disease, and the crisis of the pneumonia was followed by an elevation of the acidity which persisted. The cause or causes for such changes are not known.

The Absorption of Fat Through the Skin of the Newborn Rat.—W. H. F. ADDISON and D. A. FRASER (from the Department of Anatomy, University of Pennsylvania). The clinical use of ointments and salves dates from ancient times, but the study of how fat is absorbed is a recent one and is still incomplete. According to current conceptions, when a fatty substance is rubbed on the skin it is partly pressed into the hair follicles and sweat glands, and absorption takes place chiefly through the epithelium of the sebaceous glands and of the ducts of the sweat glands. In order to study histologically the absorption of fat through skin, newborn rats were used. In these there are no sweat glands, the hairs have not yet appeared and the hair follicles are in an early stage of development. In the epidermis there are already differentiated three strata—corneum, granulosum and germinativum. In the stratum corneum is a variable number of layers of swollen empty cells, as in the fetal skin. In the granulosum are three or four rows of cells, with numerous keratohyalin granules at the poles of the horizontally-directed nuclei. The stratum germinativum is also three or four rows in thickness, and forms a uniform zone, except where it is continued inward as the developing epithelial hair follicles. The underlying connective tissue is highly cellular and contains many vessels.

When lanolin is applied to the skin of newborn rats it passes through the cells of the epidermis into the tissues of the corium. At the end of a half hour it can be demonstrated histologically by fat stains in all these tissues and apparently in the superficial bloodvessels. In order to see whether the fat within the blood was possibly due to the animal having suckled, the blood of animals to be experimented upon was first examined by the darkfield microscope. In animals which had suckled there were numerous chylomicrons in Brownian motion within the plasma, but in animals which had not suckled no chylomicrons were seen.

Our observations show that in the skin of newborn rats there is direct absorption of fat through the surface epithelium into the deeper tissue. In accordance with current theories of the nature of plasma, membranes

and protoplasm, it is indicated that the fat probably passes in by spreading along the lipid protein interfaces of the protoplasm of the cells.

Afferent Nerve Impulses from Muscular Receptors.—G. P. McCouch, A. FORBES and H. L. RICE (from the Laboratories of Physiology of the Medical School of the University of Pennsylvania and of Harvard University). Afferent nerve impulses from muscular receptors were recorded from the peripheral portion of the cut peroneal nerve of the cat by FORBES, CAMPBELL and WILLIAMS (*Am. J. Physiol.*, 1924, 69, 283). The stimulus employed was the contraction of the tibialis anticus muscle in response to a single break shock to the nerve. Three oscillations (designated *b*, *c* and *d*), due to groups of proprioceptive impulses, followed the stimulating action current.

The object of the present work was the correlation of these groups of proprioceptive impulses with changes in the muscle. Records were made under both isometric and isotonic conditions. Action currents from nerve, tension upon the tendon and movement of the foot were synchronously recorded upon the same film. The time relations and a comparison of the amounts of tension, of movement and of action currents developed under various degrees of limitation of movement indicate that the *b* wave is associated with initial rise of tension; the *c* wave is associated with movement; the *d* wave is associated with the rise of tension occurring at the terminal slowing of movement, when the momentum of the descending foot puts the flexor tendons upon a stretch.

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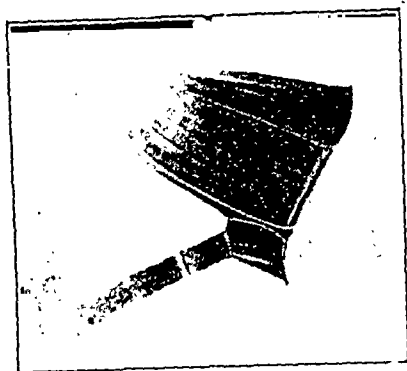
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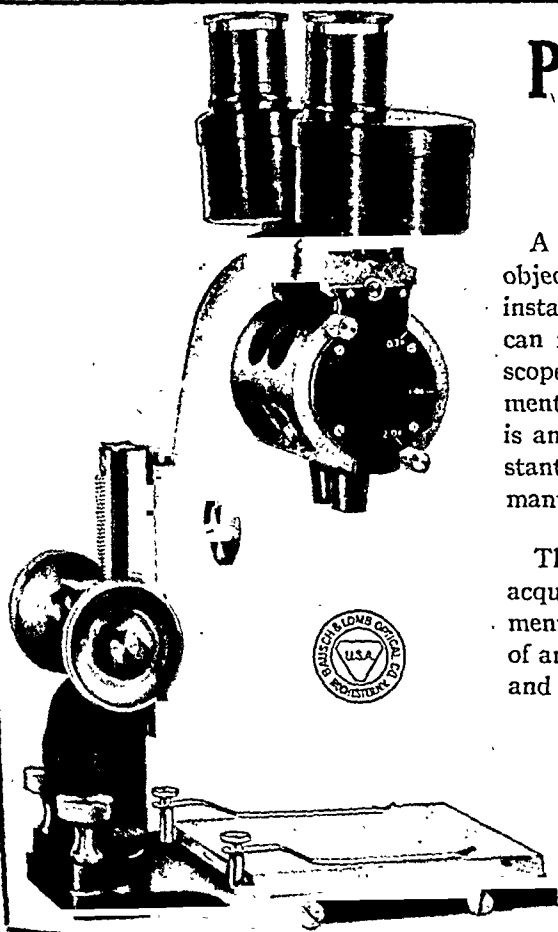
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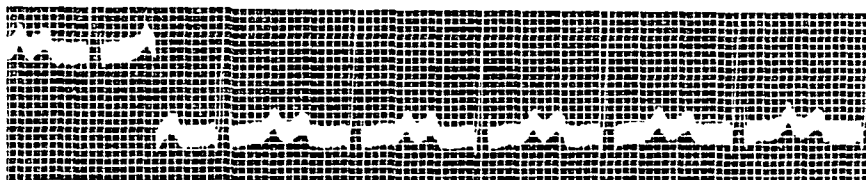
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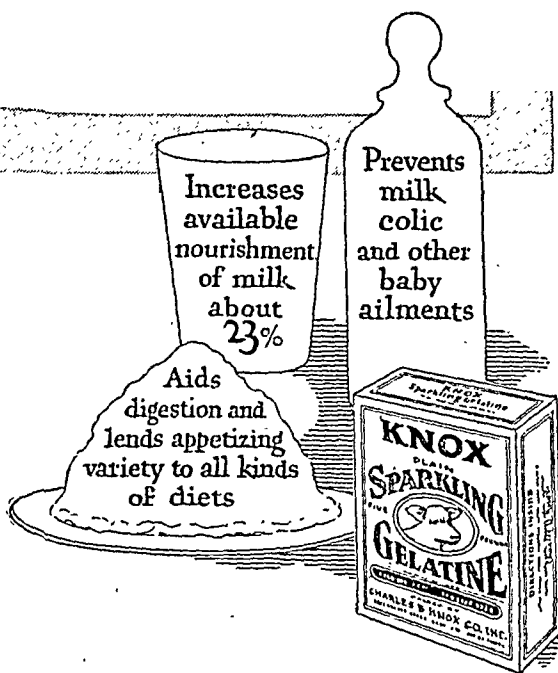
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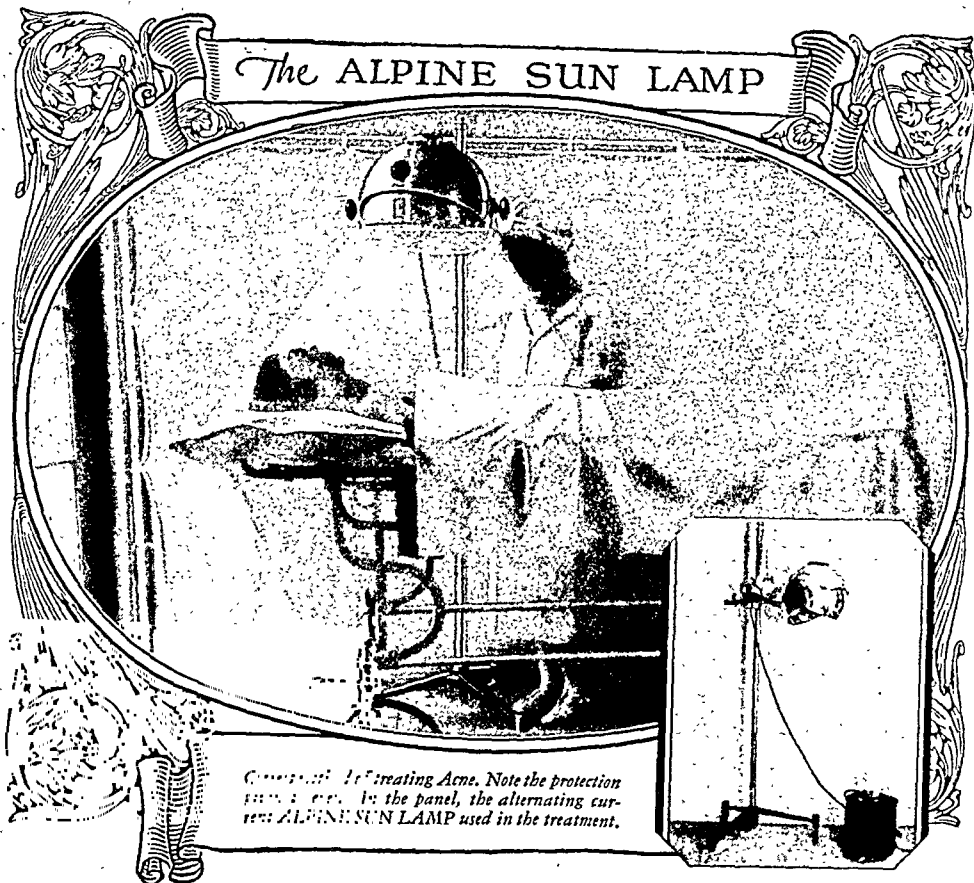
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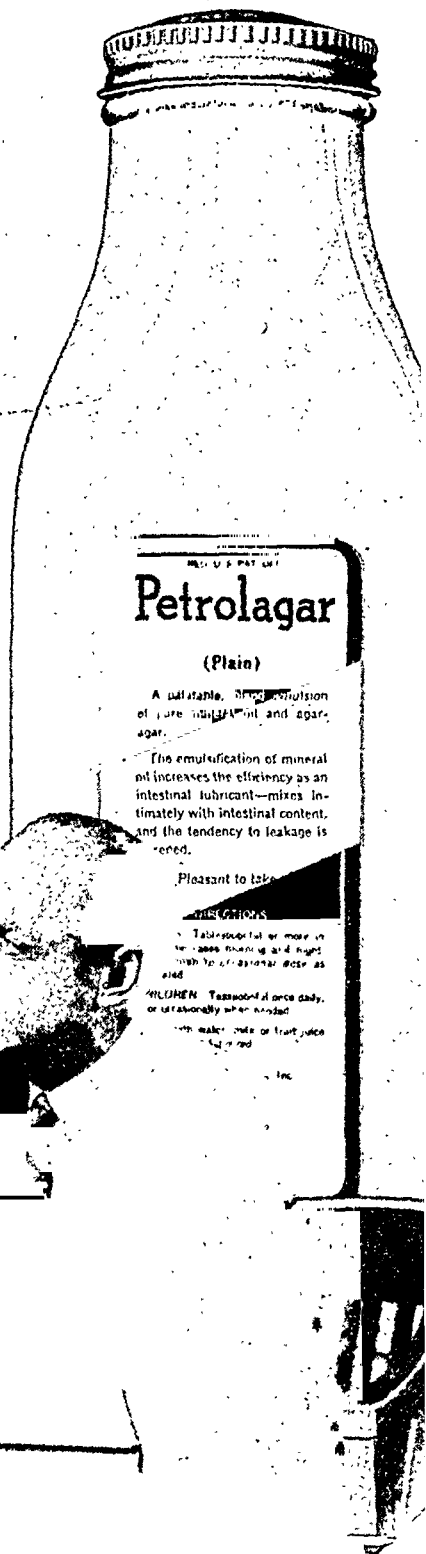
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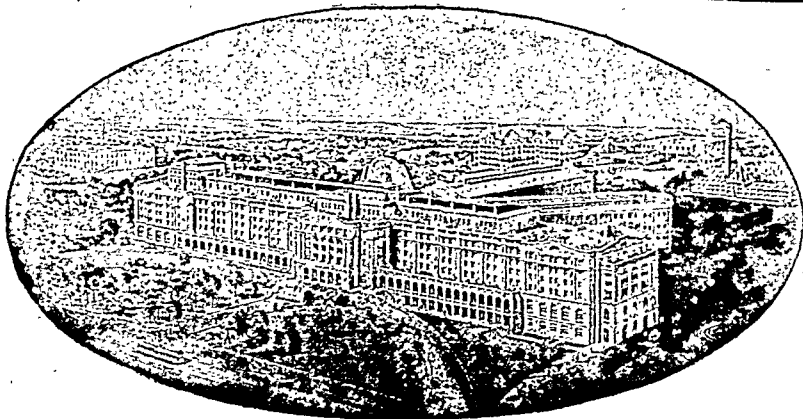
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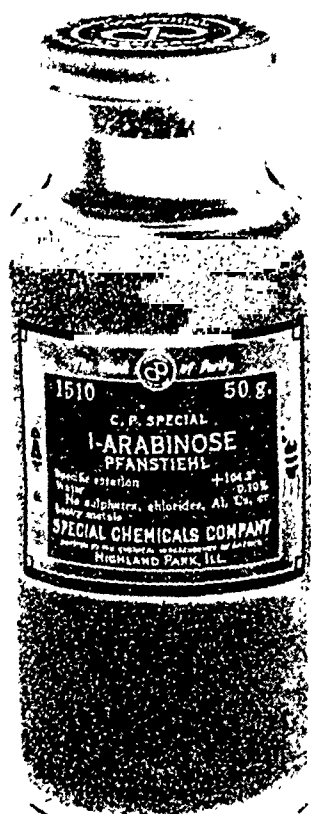
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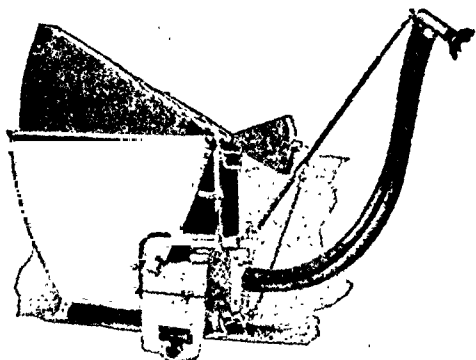
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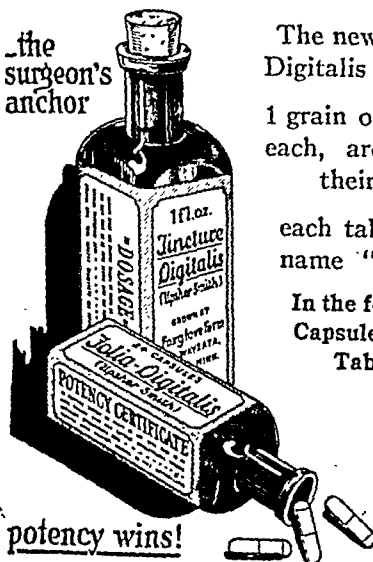
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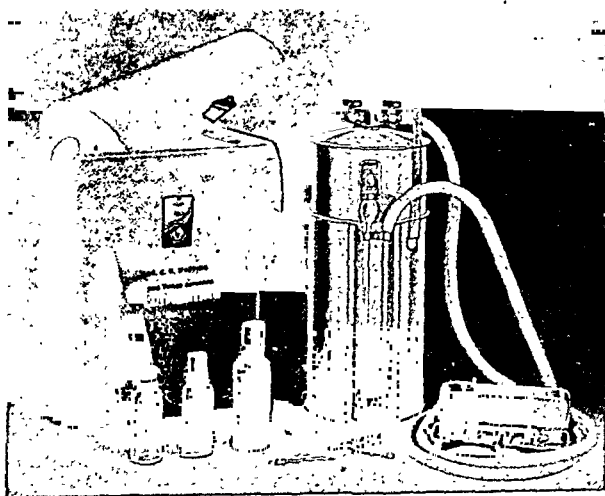
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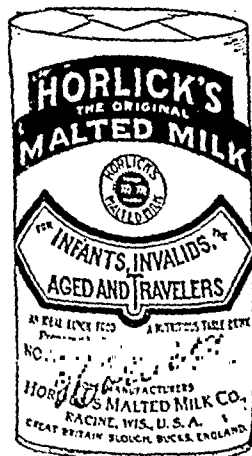


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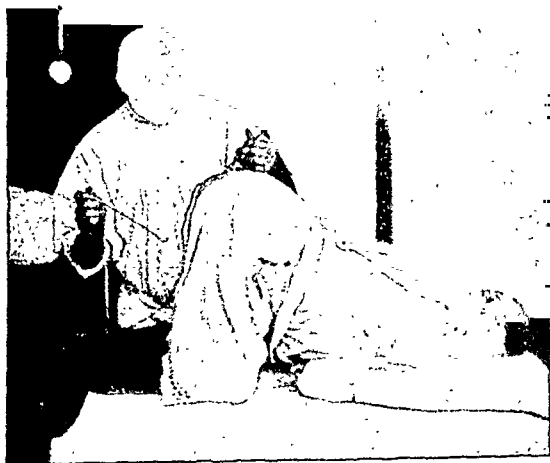
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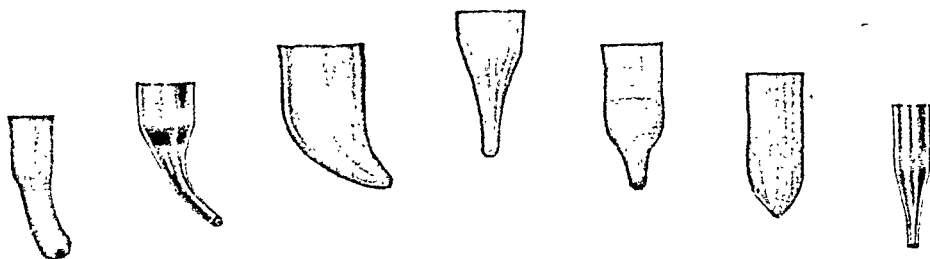
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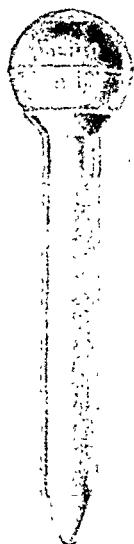
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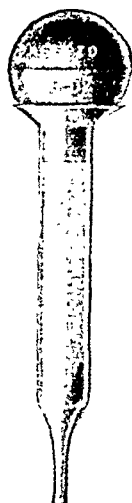


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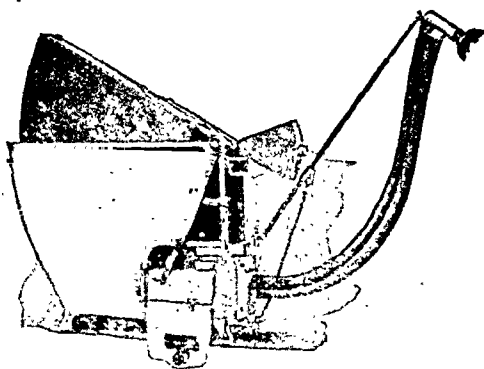
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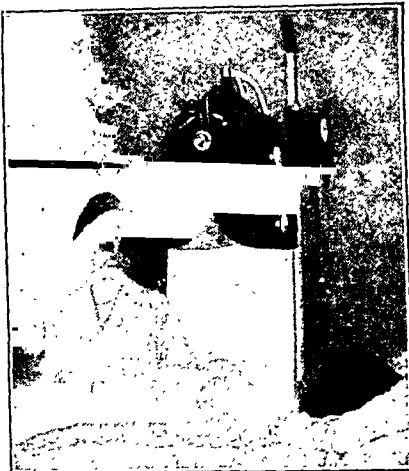


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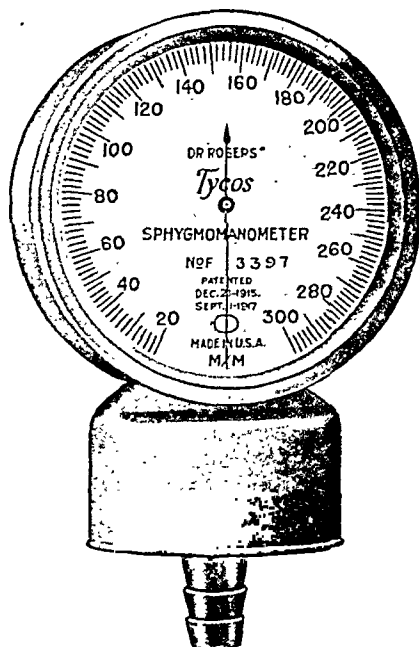
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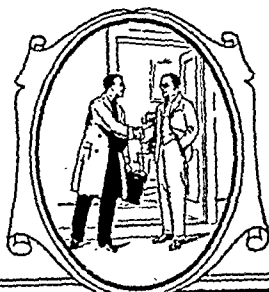
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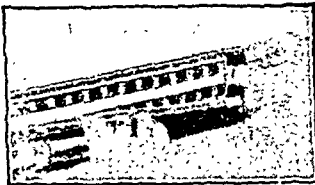
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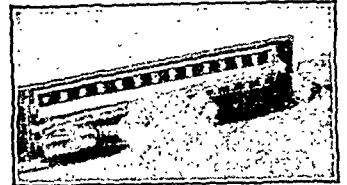
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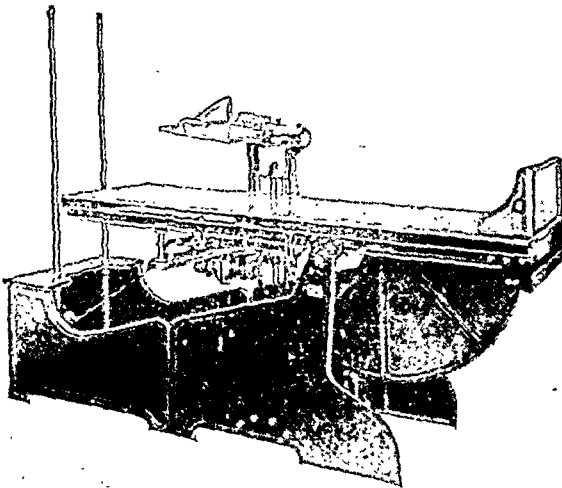
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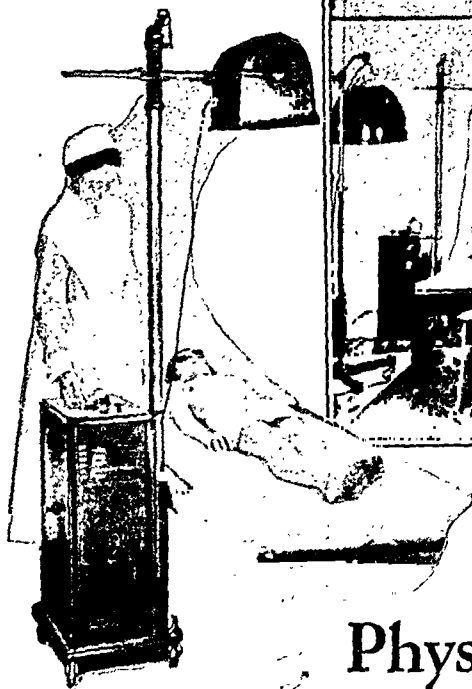
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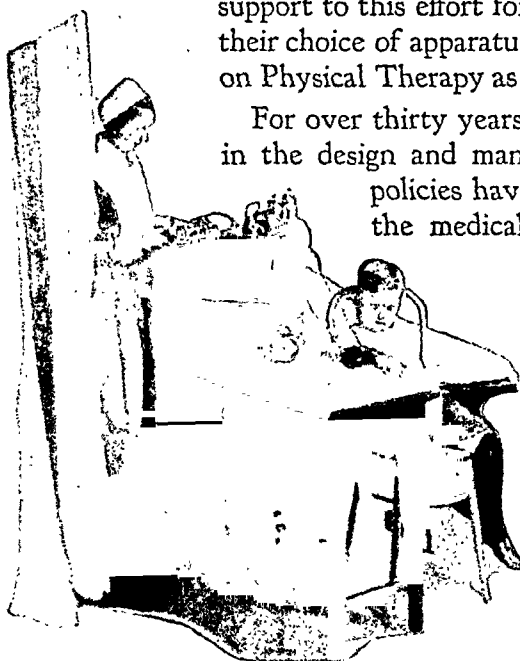


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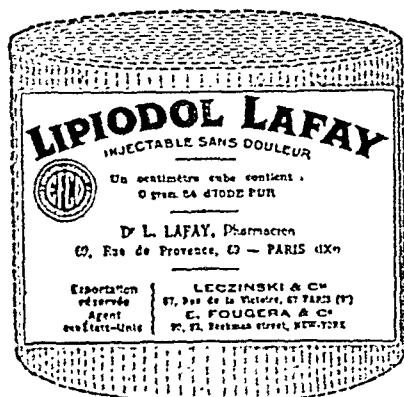
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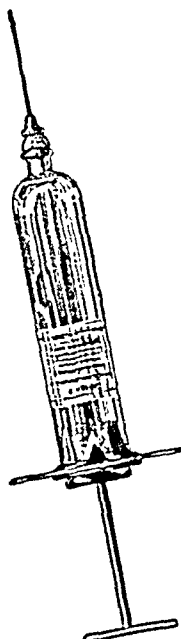
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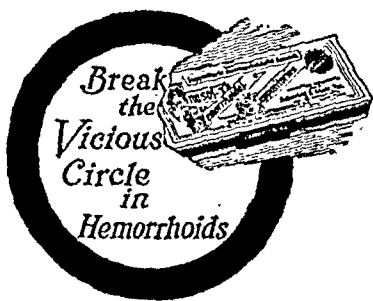
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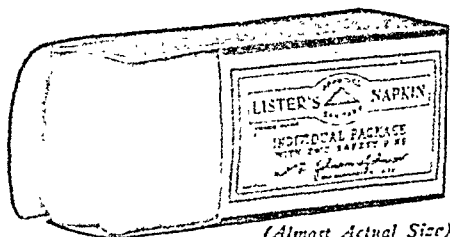
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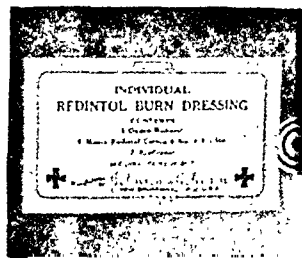
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PHILADELPHIA.

(From the Henry Phipps Institute of the University of Pennsylvania and the Moore School of Electrical Engineering of the University of Pennsylvania.)

A DESCRIPTION of the method of synchronizing Roentgen-ray exposures with selected phases of the cardiac cycle, and a brief preliminary report of some deductions from such exposures, has already been given.¹ Since that report the Weyl pulse relay has been routinely employed in studies of the chest of both adults and children at the Henry Phipps Institute. Some 4200 additional exposures confirm the early estimate of the value of synchronization.

Roentgenograms of excised lungs have been used both as a check and as a standard of detail and contrast to be sought in films of the living. Excised lungs, if free from marked consolidation and edema, can be inflated to secure the fullest detail and contrast of normal structures and pathologic changes. They constitute, thus, an ideal which is unattainable during life, in so far as the presence of the chest wall and the function of the heart and vessels mar detail. The thickness of the chest wall is a slight factor, particularly in thin children and young adults. It requires only about 20 to 30 per cent more ray than is used on excised lungs to secure from the average adult, films of similar photographic effect. To some extent it would

seem that the slight edema commonly present in the lungs of persons dying from other than sudden causes offsets the effect of the chest wall in blurring detail.

The direct and indirect effects of cardiac activity have not attracted the attention they deserve in estimating the causes of blurred pulmonary roentgenograms. It is true, the trend of roentgenology is toward shorter exposures, those of a second or more giving way to those of a tenth and a twentieth, then to a fortieth and a sixtieth. And in general the faster the exposure the greater the number of those films showing a rich trunk shadow arborization uniformly throughout the lung field. But those who are accustomed to examine their films not only stereoscopically, but each film of the pair separately, and to compare one with another the first and second films of the pair, realize that it is common to find the trunk shadows are not equally sharp in both exposures. For example, in exposures as short as 0.05 second, one film of the pair may show the hilum and descending trunk shadows sharply and many branches may be defined, arising from the main stems and traceable well out to the periphery; in the other film, the whole hilum shadow and the main branches may be blurred and the peripheral arborization quite indiscernible. Such disparity is not uncommon in stereograms. If such a pair of films be examined stereoscopically, the blurring of the one film will usually be read into both and may be interpreted as pathologic in origin. Yet careful examination of the heart outline will give the clue to such inequality of detail. For it may be seen that the contour is different in the two exposures and the blurring referable to systolic movement.

Verification of this may be obtained from synchronized exposures whereby stereoscopic pairs, alike in all respects, can be made. If the exposures are synchronized to occur in late diastole, the trunk shadow arborization is sharp and well defined to the periphery. If the exposures are synchronized to occur at the beginning of systole, the hilum shadow and trunk arborizations are blurred and ill-defined. Such diastolic and systolic stereoscopic pairs of films, made on the same individual on the same day, leave no question that the cause of the blurring of hilum and trunk detail is not pathologic.

When exposures made in late diastole, that is as far as possible after the effect of systolic movement, are compared with films of excised lungs, the vessels of which have been tied off before excision and are therefore filled with blood, it is apparent that even more rapid exposures (0.02 second) fail to record all the vascular and bronchial arborization that can be shown in the excised specimen (Figs. 1 and 2). The trunks that are particularly lacking in the living are those directed toward or away from the eye, viz: the target. This is partly assignable to optical difficulties in the perception of structures seen in perspective. But it is also clear, on careful examination of the shadows of trunks running in planes nearly perpen-

dicular to the ray, that many of these recorded in films of the excised lung are lacking in films of the living. There appear to be two possible explanations of this difference. First, displacement or alteration of the curve of the trunks due to the effect of changing pressure in the curved, branching arterial tree. This would postulate that the fall in pressure in the pulmonary arterial circulation is sufficient, even in the latter part of diastole, to cause the artery and concomitant bronchi, and to a less extent, and indirectly, the veins, to move slightly but enough to render many shadows too thin to be traced out from the main stem to the periphery, even when exposures are as short as 0.02 seconds. Of course the complexity of the branching would allow such changes in position to occur in many planes; and there may thus arise segmentation of shadow lines enough to account in part for the lessened visibility. The other possibility is that the sudden ejection of blood into the distensible arterial tree, distributed in the elastic lung, is sufficient to set up a rapid vibration, the period of which is higher than the speed of exposure, and sufficient in amplitude to render the shadow imperceptible. There is little doubt that both factors are operative, since both are necessary results of the hydrostatic and elastic factors present, and whatever their relative importance, we believe from our study that they are material and explain much of the difficulty of recording many branches of the vascular and bronchial trees.

It seems probable that displacement is the cause of the blurring of the large trunks, especially of those running to the base, and that rapid vibration is the greater factor elsewhere. For in the inner third of the lung the vessels are large relative to the contiguous air-bearing tissue. Vibration is more likely to be set up when the trunks are surrounded by a relatively large volume of a highly elastic medium. And toward the middle and outer thirds the air surrounded by the elastic lung substance is peculiarly suitable to sustain vibratory impulses.

The evidence in favor of these views comes from several sources. Films synchronized with early systolic discharge show more blurring of the right descending trunk shadows than those exposed at other cardiac phases. While it is impossible to rule out cardiac volume changes, the auricle is usually at rest when such exposures are made, and ventricular systole, assuming a total output of 75 cc.² in 0.15 seconds actual discharge time, would amount to not more than 13 cc. with exposure of one-fortieth of a second, the average we have used for children. This blurring occurs throughout the inner third of the lung field and since these vessels are under increasing pressure during this exposure, it appears that the major part of the disturbance is due to displacement. At this phase the peripheral markings are almost unrecognizable but are segmented in appearance as well as blurred, probably the composite effect of vibration and displacement.

Exposures have also been made in mid or late systole, that is when the pulse, of which the velocity averages about 6 meters a second,³ has had time to reach the periphery. The pressures from the heart to the capillaries are then established at nearly a constant value, and displacement is therefore slight. Blurring in midsystolic films is less than in early systolic exposures, although cardiac output is not less. When midsystolic films are compared with diastolic exposures, it is seen that in the midsystolic films the trunk shadows of and near the main stems are only slightly less definite; but those in the middle and outer thirds are fuzzy and less clearly traceable throughout the lung fields. It is difficult to know what might cause such appearances in the middle and outer thirds, other than vibration set up by the pulse wave.

Further evidence in support of this explanation is obtained from other sources. In the same individual on the same day stereoscopic pairs were made in late diastole, first with a pulse rate of 66 then with one of 84. In the former pair of films, the trunk shadows were more clearly defined, more numerous and could be better traced branching out to the periphery. The better detail was unmistakable in the flat film and even more noticeable stereoscopically. While the period of vibration will be influenced by individual variations in the pulmonary structure (pulmonary elasticity, length and condition of vessels) and the tension due to the amount of inspired air, the amplitude of vibration will always be less the later the exposure falls after the exciting pulse wave. This explanation also accounts for the observation that films of different individuals of the same general chest size, muscular development and subcutaneous fat, all of which are estimated in calculating exposure, vary in photographic detail in rough correspondence with pulse rate, which is recorded for purposes of synchronization. This general correspondence is modified decidedly by two factors which decrease the elasticity of the lung, namely age and emphysema. Comparison of films of young adults with those of old persons of the same chest size and nutrition shows a marked increase in the number and prominence of trunk shadows in the latter. Films of individuals beyond middle life show that a gradual increase in photographic detail occurs with age, apart from signs and symptoms of emphysema.

It is indisputable that, both with age and with emphysema, lessened density of the pulmonary parenchyma affords a basis for sharper contrasts whereby the vascular and bronchial arborizations stand out. But there are indications that this is not the sole, perhaps not the major factor. (1) If it were only a matter of relative densities one would expect that over-exposure would wipe out a large part of the increased pulmonary markings of films of the emphysematous as it does the dense, though less sharp and less contrasting trunk markings, in films of normal individuals with slow pulse rates. But the persistence of sharp detail out to the periphery, despite

variations in the quantity and hardness of ray, is characteristic of the films of emphysematous individuals. (2) There is much less fuzziness and lost detail in the arborizations shown in systolic as compared with diastolic exposures of the emphysematous, than occurs in films of the normal chest. This indicates that the amplitude of vibration is damped. (3) Even with rapid pulse rates, films of emphysematous patients show throughout the lung field a sharpness and richness of arborization which is almost as fine as that seen in films of the excised lung. (4) An increase in pulmonary density due to slight edema in the excised lung fails to cause a definite loss of trunk markings comparable to the decreased basis for contrast; this is, of course, just a reversal of the effects of the wasting process to which has hitherto been assigned the prominence of trunk markings in the films of emphysematous persons.

Emphysema constitutes a generalized pathologic change recognizable roentgenographically by uniformly increased prominence of trunk markings throughout both lung fields. Complimentary evidence of the importance of vascular vibration is secured from localized infiltrations. Here the process is one of increased pulmonary density with loss of elasticity and therefore lessened expansibility and retractability. Yet prominence of the trunk markings leading into tuberculous infiltrations is a roentgenologic characteristic both in the early, fresh, and in the old, more or less healed, lesions. Apparently solely on the basis of roentgenograms, it has been common to refer such visibility of trunk shadows to peribronchial tuberculosis or peritrunkal tuberculous lymphangitis; conceptions which find no material basis in pathology. Postmortem, arteries, veins and bronchi may be the only recognizable pulmonary constituents in widely excavated or indurated areas; but when infiltrations are slight or moderate, selective deposition of tubercles about bronchi and vessels, *especially those which are large enough to be recorded in the roentgenogram*, does not occur. Nor can there be seen, on section of such infiltrations, any increase, uniform or irregular, in the thickness of the trunks of supply or their areolar sheaths. And in films of excised lungs those trunks leading to infiltrated areas are no more prominent than those elsewhere in the lung.

The evidence that the abnormal prominence of trunk shadows is chiefly due to decreased pulmonary elasticity rather than to changes in relative density of the pulmonary structure, receives an addition in a few chest films of patients with mitral disease sufficient to cause slightly impaired pulmonary circulation. In these there is an increase in the number and breadth of the main trunks, and the branches of many trunks, chiefly venous, because traceable into the auricle, could be followed further peripherally than in the normal but nothing was seen approaching the detail in films of the emphysematous patients.

Broadening and fuzziness of the hilum and trunk shadows has been ascribed to bronchitis and to the respiratory manifestations of many diseases of childhood, both during the acute stage and after the cessation of symptoms. It has further been held that the residua of repeated respiratory infections are responsible for the increased number and prominence of trunk shadows toward the age of maturity. We have examined by synchronized exposures many children, both during the acute stage of bronchitis and after the acute infections of childhood, without being able, in the absence of bronchopneumonia, to distinguish any change in roentgenographic appearances. Parenthetically, it may be noted that bronchopneumonia causes only localized changes, both the familiar irregular densities due to the consolidation and prominent trunks referable to localized lessened parenchymal elasticity. The local prominence of trunks persists for a varying period after a clearing of the recordable densities due to bronchopneumonia, but usually entirely recedes except in tuberculous cases. We believe this gradual recession to be due to slow recovery of pulmonary elasticity. Many cases of severe bronchitis have been examined without our being able to distinguish between films taken before and during the attack. On the other hand, by synchronizing exposures with systole, it is possible to produce in healthy individuals the broadening and blurring of the hilum and larger trunk shadows to which has been attached a pathologic significance; while in diastolic exposures of the same individuals, blurring is absent. The elevated heart rate of acute infections has, we believe, helped to cause confusion in films of children, because extensive blurring occurs more frequently, especially when exposures are not synchronized, than in films of the same child with the slower pulse of health. Films of excised lungs showing on section indications of severe bronchitis have been carefully examined but we have not been able to recognize uncomplicated bronchitis in the film. Even bronchi filled with pus have not been distinguishable from vascular shadows in the otherwise healthy lung; and section of the bronchi and vessels of adult lungs done by Dr. Opie failed to reveal evidence that fibrous tissue is laid down about them. Nothing denser than areolar tissue surrounding the vessels and bronchi was seen in the absence of chronic bronchitis and bronchiectatic change. The increase in the number of trunks recorded as maturity approaches appears to be due to the slower pulse rate and the greater length and diameter of the trunks.

In films of the excised healthy lung, the vessels of which have been tied off before excision, the shadows of the bronchi and vessels form a very close mesh-work (Fig. 1). The shadows of artery and vein are of practically uniform density from margin to margin; the bronchus, an air-containing tube, is recorded as two narrow branching lines separated by a clear space. The vascular shadows are denser,

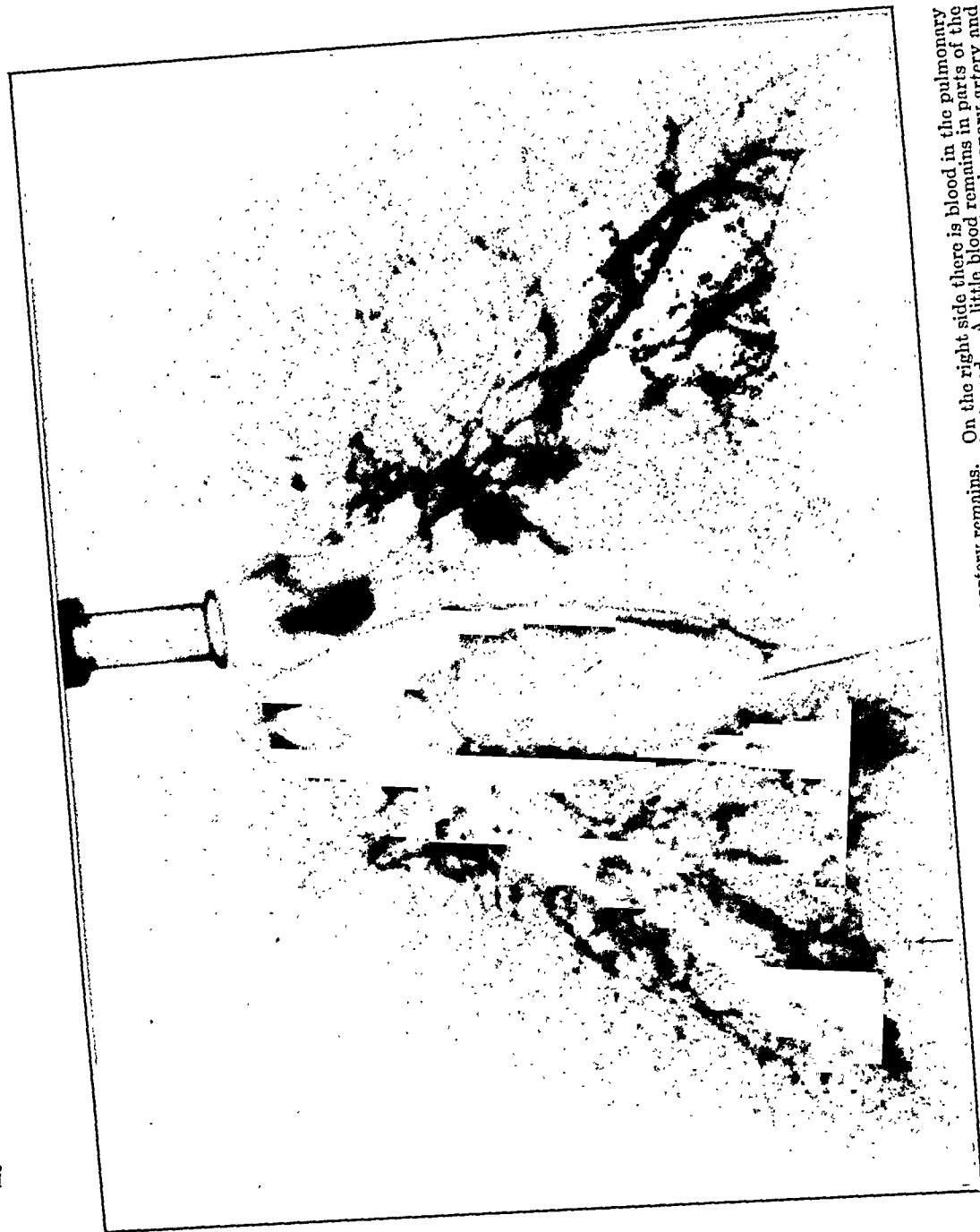


FIG. 1.—The aorta was not removed, and part of the pulmonary artery remains. On the right side there is blood in the pulmonary vein, the main stem lying medial and inferior to the bronchus. Many branches can be traced. A little blood remains in parts of the arterial tree, but the greater part of the unclothed blood ran out on inflation. On the left there is blood in both pulmonary artery and vein. The main stems of both can be seen and a few branches can be distinctly traced to the periphery in the lower part of the lung shadow. For the most part, the number of branches of both vessels, and their repeated crossings, render identification difficult. The on the right, where only the vein shadow is heavy, few bronchi can be seen except the large branches arising from the main stem. The appearance spoken of as beading of trunks, due to branches arising more or less axially to the incident ray, is fairly well reproduced in both bases. One such trunk near the left margin is marked with an arrow. The beaded appearance is not so conspicuous in the apex because the vascular relaxation permits the blood to run into the basal trunks. These lungs were normal on section.

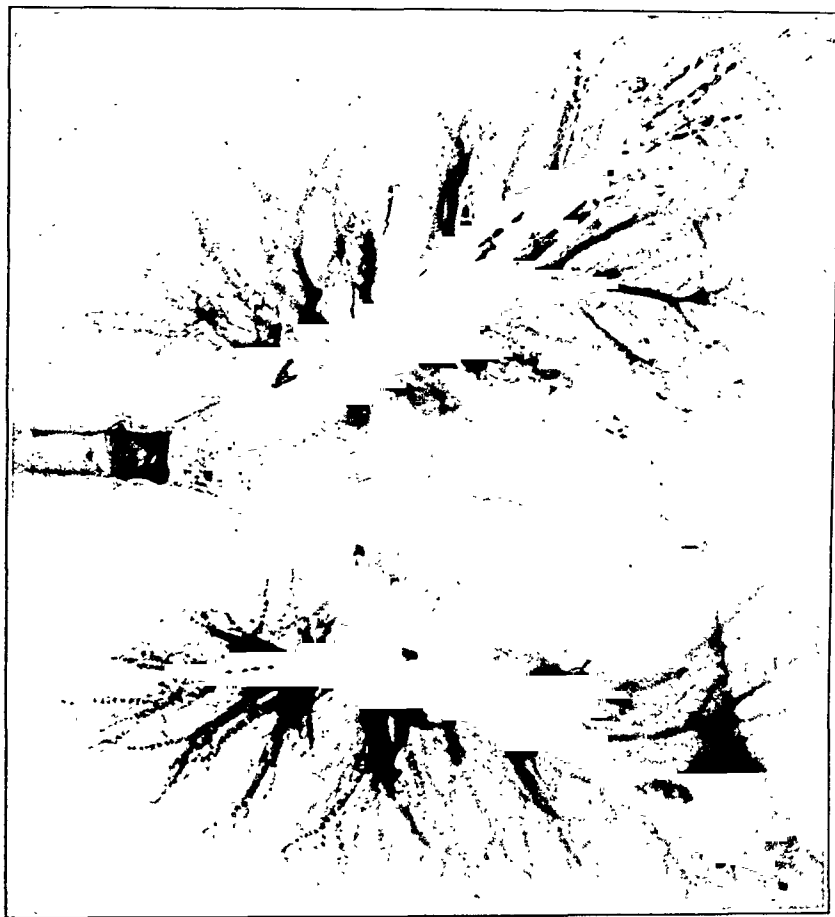


FIG. 2.—Same specimen as Fig. 1. The right and left arteries were injected with bismuth in gelatin, giving a homogeneous shadow and allowing the ascending branches to be seen. The bronchi were inflated with bismuth powder, the resulting shadow being an intensification of the wall on the right, a granular shadow in the left upper bronchi and an almost homogeneous shadow in the left lower bronchial branches, denser than that of the artery. The injections went farther into both artery and bronchus on the left side, although the artery is well seen in the right upper lobe. It is apparent that in films of the living all branches are not recorded. When the veins are also injected there is an indistinguishable dense tangle of branches obscuring most of the lung field.

stand out more prominently and blot out the bronchial shadow when they intersect; and since the shadows of all but the larger bronchi are crossed by many vascular shadows, it is difficult to trace the bronchi past the middle third. A few can be followed out to the outer third but not nearly so many bronchi can be traced as can arteries or veins. In lungs showing even slight bronchiectasis, or in emphysematous lungs with chronic bronchitis, the irregularity of outline and of thickening of the bronchial wall gives a shadow that is more easily traced. In films of the excised lung this is very noticeable. In the living, decreased elasticity, local as in bronchiectasis or general as in emphysema, contributes to the better visibility of bronchi.

Careful study of synchronized films shows that the characteristic bronchial shadow is relatively rare beyond the inner third. Except for the large arterial trunks directed toward the diaphragm, the majority of the branching shadows, especially in the upper two-thirds of the lung field, can be traced back, medially, across the shadow of the bronchus to the lower lobe, and if the patient is slightly rotated with the right side away from the film, many of these shadows may be followed, on the right, to the auricular outline. The evidence thus obtained by tracing the more prominent trunks to their source is in accord with the evidence given that there is material displacement and vibration set up by systolic discharge. The arteries (and the bronchi) are more affected, move more, and are less easily recordable than the veins.

From the above observations we think that the significance of prominent trunk shadows must be considered in the light of pulse rate, age, and the extent and situation of the area in which they appear. In young adults, uniformly prominent branchings will usually be found associated with slow pulse rates. After middle age, such prominence, especially if it extends to trunks directed toward the eye, and if it occurs even with rapid pulse rates, suggests emphysema. Both displacement and vibration are more effective in preventing perception of the trunks which run axially, or at an acute angle, to the incident ray, because displacement or vibration of these in any plane occurs across the line of ray. On the other hand, displacement or vibration in those trunks running more or less perpendicularly to the incident ray, must occur predominantly in the same plane perpendicular to the ray in order to move the trunk across the line of the incident ray.

Trunks running to the anterior part of the lung, especially veins, are more frequently seen than those supplying the posterior part of the lung. It seems possible that several factors may contribute to this: smaller lung volume limiting vibration, much as it does in the apex; decrease of caliber anteriorly running along with decrease of ray penetrability, instead of the reverse relation, which obtains posteriorly; the fact that optical perception of receding trunks is

better than that of approaching trunks; and the fact that, for any amplitude of vibration, the resultant blurring of the image of the vibrating object is greater the farther the object is from the film, viz., the nearer it is to the source of ray.

The interpretation of localized prominence of trunk shadows as due to locally decreased pulmonary elasticity, is definitely of clinical value, if prominent shadows are recorded in films in which the patient is accurately and symmetrically placed. The apices for example, cannot fairly be compared when rotation exposes one more than the other. For corresponding trunks are recorded in different planes and trunks shown medially in one film may appear centrally in another. As has been pointed out above and elsewhere,⁴ the angle at which a trunk is exposed is of decisive importance in determining the amount of detail recorded. If the patient's position is symmetrical, prominent and detailed trunk shadows in a part of a lung field adumbrate the onset, resolution or residuum of infiltration, the constituents of which in the parenchyma may be too slight, discrete or irregularly deposited to be clearly recognizable. The increased detail and stereoscopic reinforcement of synchronized diastolic exposures not only allow one to perceive more accurately such localized changes, but, by recording trunk shadows chiefly as continuous branching lines rather than segmented as they frequently appear in exposures which are systolic, distinguish the symmetrical, if prominent, trunk shadow arborization from the irregularly distributed linear, blotchy or dotted shadow of infiltration. We think that even in the apex the finer detail of synchronized exposures enables one better to record scant and discrete infiltrations. But a greater usefulness lies in the clarity with which it defines the localized or diffuse nonapical tuberculous infiltration of the infantile type. Such a lesion may, of course, occur at any age but essentially results from the slow progression instead of the healing of a primary pulmonary localization.⁵ The individual dots comprising the mottling may, in the early stage, be discrete and so soft that they are not recorded except under the most favorable technical conditions. Sometimes a slight infiltration is recorded as an irregular noded network of which the component strands are unequal in length and breadth, and irregularly beset with dots of unequal size. Either of these appearances may remain unperceived when the trunk shadows are not clearly and continuously traceable and therefore distinguishable from faint abnormal densities in the same area. If an infiltration is somewhat denser and sufficient to cast a soft shadow in which the trunk markings are only faintly distinguishable and look blurred, which is not uncommon in films of the infantile type of tuberculous lesion, the diagnosis may be made if the delineation of the trunk markings is clear in comparable areas; or in adjacent areas, except that the best comparison for one apex is the other. One can then be sure that the haziness about

the trunks in the affected area is not an artefact due to systolic movement.

The pathologic variations occurring during the prolonged clinical course of these lesions will often not be recognizable unless the normal structure in areas not infiltrated is recorded at each examination to serve as control. Such variations may be wide for years after the cessation of the infecting contact. They correspond to fluctuations in pathologic activity, often precede changes in clinical condition, and require close oversight in order to direct the therapeutic course. This is of special importance in young children for whom home treatment is desirable during a large part of this illness, which in them is peculiarly liable to smoulder protractedly despite every care.

The diagnosis of these cases may rest largely on the roentgenogram. The physical signs are commonly equivocal, rales being often inconstant, and extending over only a small part of the affected area. Changes of percussion note and of the whispered voice are sometimes not found over these lesions, and often bear no definite relation to the extent and intensity of the physical density obstructing the Roentgen ray. The tuberculin reaction is commonly intense in both manifest and latent lesions and is often the one other valuable indication of tuberculous disease.⁶ It is difficult to attach too much importance to the earliest possible recording and recognition of tuberculous lesions, whether manifest or latent, apical or infantile in type. The frequency of relapse even in technically minimal cases, does not encourage avoidable procrastination in diagnosis. The added months of sanatorium care due to involuntary delay in arriving at a diagnosis are costly enough to render economically justifiable more exacting methods.

Synchronized exposures are valuable in the differentiation of early bronchiectasis. Very small lesions may be detected when the stereoscopic reinforcement is at its maximum.⁷ We have found that in moderately advanced bronchiectasis, blurring of the lesion occurs in one-fortieth second exposures if they are synchronized with systole. There is definitely clearer detail in late diastolic films.

It has seemed to the writers that the evidence that vibration is set up by the pulse wave, although it has been obtained during fixed inspiration, may have certain physiologic implications during unarrested respiration. While the frequency and amplitude of vibration set up by any one pulse wave must be dependent on volume and tension of both artery and enveloping parenchyma and therefore must be damped by the change in tension due to progressive inspiration or expiration, vibration may produce some agitation and mixing of the air which flows and ebbs at only one point of a multilocular chamber. The respiratory value of such vibration would largely depend on its amplitude. This would vary with the size

of the pulse wave, and the sharpness of rise and fall of pressure due to its passage, for these correspond to the weight and sharpness of a stroke that excites vibration. The circulation and structure of the lungs seem peculiarly adapted to the maintenance of such vibration—low diastolic arterial pressure, sharp and large pulse pressure changes, and an elastic pulmonary parenchyma which can both receive and sustain vibration.

Conclusions. There is evidence that cardiac movement and vascular pulsation cause more extensive and complex pulmonary movement than has hitherto been recognized. The effects of vascular displacement and vibration in the blurring of roentgenographic detail are important. Artefacts are produced to which have been given a pathologic interpretation. By synchronization of exposures with late diastole, such artefacts may be eliminated and finer detail, both normal and pathologic, recorded, with marked enhancement of stereoscopic accuracy. The method is of value in the early recognition and differential diagnosis of discrete tuberculous infiltrations, especially those which are infantile in type, beginning bronchiectasis, bronchopneumonia and other processes manifesting themselves by changes in the relative density of the pulmonary structures, with slight and equivocal or no physical signs.

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ROENTGENOLOGY AS AN INVESTIGATIONAL FIELD IN THE MECHANISM AND DIAGNOSTIC SIGNIFICANCE OF PHYSICAL SIGNS OF THE CHEST.

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THE use of roentgenology in the diagnosis of certain pulmonary affections has long been established. The value of serial roentgenograms in the prognosis as well as in the therapeutics of pulmonary tuberculosis cannot be overemphasized. In recent years, attention

has been drawn to the significance of roentgenology in the study of pathogenesis,¹ pathology,² and mode of healing in pulmonary tuberculosis.³ However, radiology opens a new avenue in the investigation of clinical medicine, which may eventually lead to a different interpretation and more or less complete revision of the hitherto accepted physical signs of the chest.

The discrepancy between roentgenological and physical findings of the chest has been pointed out by Heise and Sampson,⁴ Sergeant,⁵ Rieder,⁶ Fales,⁷ Norris,⁸ and many others; but in all those studies physical signs were accepted as a matter of fact and were merely compared with radiology to indicate the advantages and limitations of each of these methods of diagnosis, few concluding that radiology is only an adjunct in our diagnostic armamentarium, others claiming that radiology surpasses physical signs in many ways. In this study, I want to point out how advantageously radiology can be applied in studying the mechanism of many classic signs of the chest and their true diagnostic significance.

Until the era of radiology, all the physical findings could be checked up only at the postmortem table, and all the physical signs were interpreted in the light of the anatomic-pathologic findings. This method, known as the anatomic-clinical study, was introduced into modern medicine by Laennec. While it is true that the only way of studying the exact macroscopic and microscopic pathology of tissue is after the autopsy, one cannot but recognize the limitations of this method in interpreting the mechanism of all physical signs, inasmuch as the postmortem examination reveals only the ultimate condition of the lungs, which can in no way explain all the protean manifestations and varying physical signs observed in the protracted course of any chronic pulmonary affection. On the other hand, roentgenology while revealing only the macroscopic pathology of the lung, enables us to visualize these pathologic alterations *in vivo*, and to study their progression or retrogression in the host himself.

Furthermore, whereas the autopsy teaches us mostly the pathologic anatomy, roentgenology often teaches us also the physiologic pathology of the lung, and is therefore more important in explaining certain physical signs. Now taking into consideration that the study of roentgenographic and roentgenoscopic pathology can be made as often as desired in conjunction with physical examinations of the chest, one can easily see what new avenues this method opens into the investigation of the mechanism and significance of many of the physical signs.

In this article, I shall limit my observations to only a few of the numerous old and new physical signs of the thorax.

Pulmonary Cavities. In a previous contribution⁹ I have indicated that about 50 per cent of all pulmonary cavities lack most, if not all, the standard textbook signs of cavitation. These, so to speak,

silent cavities are of at least two types as far as auscultatory signs are concerned, which I named (a) absolutely mute, that is, such cavities over which no suspicious signs of any pulmonary lesion can be elicited, and (b) relatively silent, that is, such cavities which do not exhibit any of the classic cavernous signs but over which other adventitious sounds are heard. Since then I have observed "silent cavities" in many more cases. The relatively silent are in overwhelming majority.

There is no doubt that routine roentgenologic examination of every chest case would disclose a much larger number of pulmonary cavities than could ever be diagnosed from physical signs alone, if we adhered to the classic signs of cavitation. It is not meant at all to indicate the fallacy of auscultation, but merely to show the necessity to revise the significance of many of the auscultatory signs. A systematic application of roentgenoscopy and roentgenography, with a more close corroboration of the physical and roentgenological findings would lead to a better understanding of the mechanism and consequently the diagnostic significance of the auscultatory signs.

Stereoroentgenoscopy tells the reason for the absolute muteness of certain cavities; such cavities are found to be located, as a rule, in the center of the lung surrounded by unaffected pulmonary tissue. We must remember that the cavernous sound is a modified laryngotracheal sound produced by the sympathetic vibrations of the cavernous wall which the air entering into the cavity sets up. The smoother the walls of the cavity, the larger its dimensions, and the nearer it is to the chest wall, the more pronounced is the cavernous quality of the breath sound. Consequently, when a small cavity is surrounded by unaffected lung tissue, the cavernous quality of the sound will be either altogether absent, or somewhat modified. These various modifications of the cavernous sounds are produced by the alterations in the surrounding tissue, the size of cavity and its distance from the chest wall, which can be determined only by means of roentgenology. Certain cavities may be mute when we listen anteriorly, while posteriorly we may hear moist râles and modified breath sounds. Such a cavity when watched stereoscopically is found to be located near the posterior wall. The same holds true of cavities located nearer the anterior chest wall.

The prognosis of these silent cavities has been discussed elsewhere,⁹ and it can be told only by repeated physical examinations. Thus a large cavity which is somewhat hyperresonant on percussion, and over which no breath sounds are obtained, is of fair prognosis. Such cavities do not show any fluid levels when studied roentgenologically, which means that the walls are well fibrosed and smooth, and the afferent bronchus has been closed probably by fibrosis. This has been verified also by autopsies. The closure of the bronchus might also be produced by secreta and necrosed material, but such



FIG. 1.—The small cavity at right base was absolutely mute to physical examination; the cavity in fourth interspace of left lung revealed itself by bronchovesicular breathing and moist inspiratory râles over an area of about 2 inches, and the small cavity in the second space was suspected from the snappy inspiratory sound with moist râles heard over this area.



FIG. 8.—Roentgenogram showing right complete thorocoplasty. Subcrepitant râles heard throughout on deep inspiration only. Note also left compensatory emphysema.



FIG. 2.—Note the dense homogenous shadow at left base. Cavernous breathing was elicited over this area anteriorly and posteriorly,



FIG. 3.—Roentgenogram of same case as Fig. 2 after induction of left pneumothorax. Note the large cavity well outlined with fluid level, indicated by white arrows. (Black arrows indicate extent of pneumothorax.)



FIG. 4



FIG. 5

FIGS. 4 and 5.—Roentgenograms of a case of artificial pneumothorax taken in inspiration and expiration respectively. Note the complete compression of upper third of lung over which no breath sounds were heard, and the respiratory expansion and contraction of lower part over which vesicular breathing was elicited. Note also wide range of diaphragmatic movement.

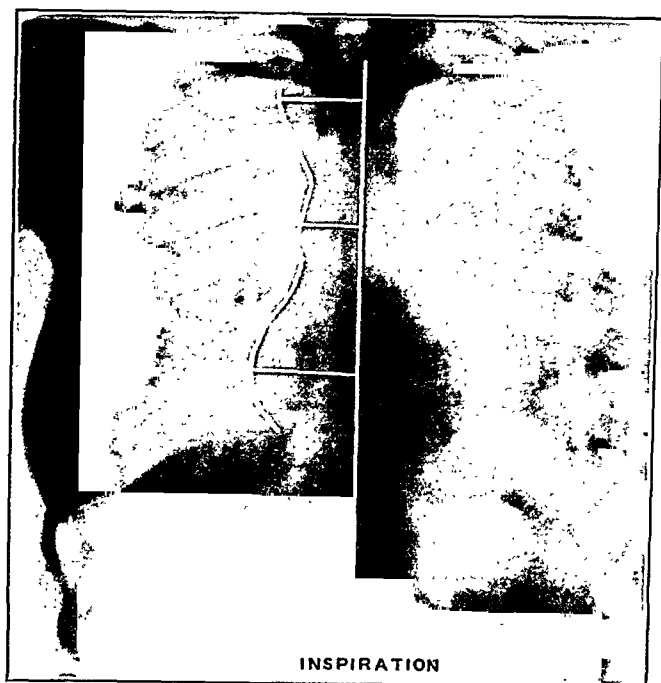


FIG. 6

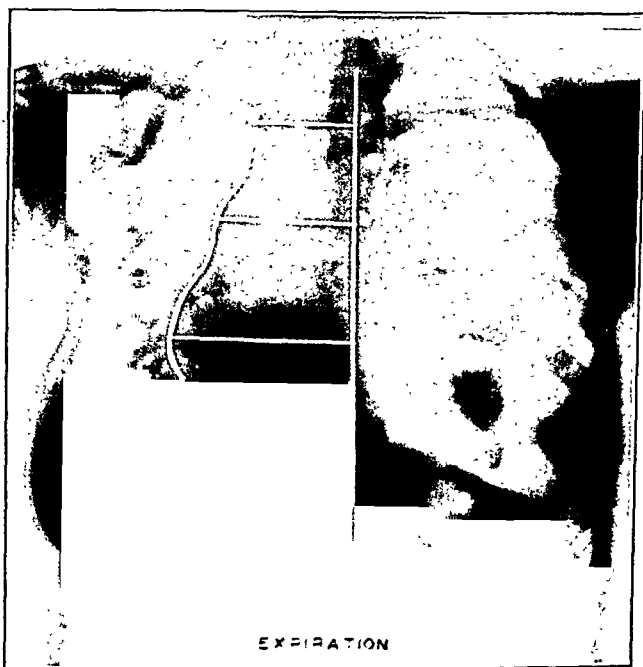


FIG. 7

FIGS. 6 and 7.—Inspiratory and expiratory plates of case of left pneumothorax. Note the pendular mediastinal movements with the respiratory phases, most pronounced at the "three weak spots of the mediastinum." A to-and-fro friction[rub was heard over the sternum anteriorly, and from fourth to ninth dorsal vertebra posteriorly.

cavities will at one time or other show a fluid level and their physical signs are very changeable. These cavities are, as a rule, of poor prognosis.

The absence of the classic cavernous breathing by no means excludes the presence of a pulmonary cavity which might easily be found on roentgenoscopy. The following findings are very suggestive of pulmonary cavity: a deep inspiratory sound over an isolated area of the chest or any other modified breath sound, with moist râles over a limited area of the chest, heard on ordinary inspiration. Fig 1 is a roentgenogram of the chest with silent pulmonary cavities of both types. The cavity seen at the right base was not suspected from physical findings as there were no adventitious sounds heard over this area, whereas the feeble bronchovesicular breathing with moist inspiratory râles heard over about 2 inches at the fourth interspace of the left chest was interpreted as a cavity and is seen plainly on the roentgenogram, and the small cavity in the second space was suspected from the snappy inspiratory sound and the moist râles heard on ordinary breathing over this limited area.

It should be noted, however, that cavernous breathing always indicates a cavity, even if the cavity is not well outlined on the roentgenogram. If pneumothorax is instituted in such a case the cavity wall comes out very conspicuously. Figs. 2 and 3 are illustrative of this. Fig. 2 does not reveal any definitely marked cavity, though pronounced cavernous breathing was heard over the lower third of the left lung anteriorly and posteriorly. Fig. 3 is a roentgenogram of the same case taken after the induction of pneumothorax; a thick-walled cavity stands out conspicuously with a small fluid level.

Pneumothorax. The constant and careful roentgenoscopy which is required in all cases treated with artificial pneumothorax has contributed a great deal to the understanding of the various physical signs of pneumothorax. The percussion signs of spontaneous as well as artificial pneumothorax range from tympany to diminished resonance, depending on the extent of the pneumothorax and particularly on the existing intrapleural pressures; the auscultation signs may vary from absent breathing or vesicular breathing to all tones of amphoric breathing; the existing sound being determined by the intrapleural pressure, the extent of collapsed and non-collapsed portions of the affected lung, and upon the existence or nonexistence of visceral pleural opening. A systematic study of the varying physical signs of a case of artificial pneumothorax in which the extent of the involved and uninvolved portions of the lung can be studied accurately before and after induction of the treatment and the intrapleural pressure can be graded accordingly, when corroborated with roentgenological findings, sheds light on the mechanism and significance of many of these signs.

In discussing the mechanism of localization of gas in the pleural cavity,^{10,11} I indicated that the difference in the elasticity of the diseased and nondiseased lung tissue as well as the difference in the intrapulmonary and intrapleural pressures make it possible for the gas introduced into the pleural cavity to localize over the diseased portion without curtailing much of the function of the unaffected portion of the treated lung. This curtailment of function is directly proportional to the intrapleural pressures created therein; when the intrapleural pressure exceeds that of the intrapulmonary pressure, the uninvolved portion of the lung will also be compressed and its respiratory surface reduced to a minimum, whereas if the intrapleural pressure is less than that of the intrapulmonary pressure, the functioning portion of the lung will continue to expand and contract with each respiratory phase. These pneumodynamic principles explain many of the physical signs of pneumothorax.

Figs. 4 and 5 are roentgenograms of a case of left artificial pneumothorax taken in inspiration and expiration respectively when both intrapleural pressures were less than atmospheric. It is to be observed that the upper diseased third of the lung remains compressed and unchanged in both inspiration and expiration, whereas the lower uninvolved portions of the lung expand and contract with each respiratory phase. This accounts for absent breath sound over the upper third of the right chest, and somewhat harsh vesicular breathing over the rest of the chest. When the intrapleural pressure was increased by introducing larger amounts of gas into the pleural cavity, which entailed a more effective collapse of the entire lung, the vesicular breathing became markedly diminished.

However, in cases of spontaneous pneumothorax amphoric breathing is present at one time or another, which varies in intensity and pitch according to the existing intrapleural pressures. As long as amphoric breathing is present the compressed lung fails to reëxpand, which indicates a visceral pleural opening. Frequent roentgenoscopy shows a gradual reëxpansion of the collapsed lung after the disappearance of amphoric breathing.

In my article on significance of amphoric breathing and coin sound test,¹² I discussed fully the mechanism and diagnostic significance of these sounds. The persistence of amphoric breathing means failure of the visceral-pleural opening to close and usually spells a poor prognosis. The gradual receding in the pitch of the coin sound is indicative of a decrease in the intrapleural pressure and a slow reëxpansion of the collapsed lung. The hyperresonance in pneumothorax is determined both by the extent of the collapse and particularly by the existing intrapleural pressure, being most pronounced when the pressure exceeds the atmospheric one, and shading into diminished resonance and even dulness when the lung is partially expanded and the intrapleural pressures are below that of the atmospheric.

Mediastinal Friction Rub. The following case is very illustrative in bringing out the importance of roentgenology in explaining certain baffling physical signs of the chest which even postmortem examinations could not solve, inasmuch as it has to do more with pathologic physiology than with pathologic anatomy.

Figs. 6 and 7 are inspiratory and expiratory plates of this case of left spontaneous pneumothorax. The intrapleural pressures at this time were $+5 + 30$ water manometer. Percussion elicited slight hyperresonance from apex to base, and breath sounds were absent, except for a faint posttussic amphoric sound, which disappeared in a few days. A peculiar to-and-fro friction rub was heard over the sternum anteriorly and from the fourth to the ninth dorsal vertebral posteriorly, resembling somewhat the sound made by moving paper back and forth between two fingers. This sound was most baffling. However, roentgenoscopy revealed the secret; the movements of the collapsed lungs were hardly perceptible, whereas the labile mediastinum was swinging from left to right, pendulum like, with each respiratory phase, reaching beyond the nipple line of the right side on expiration. The inspiratory and expiratory Roentgen ray plates show the range of the swinging of the mediastinum distinctly which, no doubt, accounted for the peculiar friction rub.

This friction rub was becoming feebler after the fifth day and disappeared completely on the tenth day. At this time the intrathoracic pressures in the left pleural cavity were both negative, the lung was markedly reexpanded, and distended and contracted with each respiratory cycle. The swinging of the mediastinum was hardly noticeable under the fluoroscope. It is obvious enough that the mechanism of production of this peculiar friction rub could have never been explained without the aid of roentgenoscopy.

Râles. Râles are adventitious noises indicative of pathologic anatomy or altered physiology in the respiratory system. They result from interference with the free movement of air within the bronchopulmonary structure, due either to intrinsic or extrinsic causes. These râles are classified according to their acoustic properties into sonorous, sibilant, crepitant and so forth; according to their mode of production into dry or moist; and according to their anatomic topography into bronchial, vesicular, and so forth. These classifications of râles are not distinct entities because there is a close interdependence between the topography, mechanism, and acoustics of the râles. The "musical" quality of the râle is not only determined by its mode of production, but also by the anatomic seat in which the respiratory pathology has occurred, hence the diagnostic value of the exact interpretation of these râles. Still; there is as yet no unanimity of opinion among clinicians as to the diagnostic significance of certain râles, and careful systematic serial roentgenography might enable us to elucidate the mechanism and clinical value of such râles.

The so-called subcrepitant râles are still the greatest bone of contention among clinicians as to their diagnostic and prognostic significance. Bushnell¹³ and others consider the crepitant and subcrepitant râles as a sure sign of clinical activity in pulmonary tuberculosis, whereas Bruns,¹⁴ adequately naming these râles "parenchymatous," claims that these are due simply to atelectasis and no clinical significance can be attached to them. No doubt, all these râles originate in the forceful separation of the walls of the atelectatic alveoli and bronchioles by effective inrush of air during the inspiratory phase, but atelectasis is an abnormal condition of the lung tissue resulting from various causes, and these latter determine the character of the râles and their relation to the respiratory cycle.

The elastic fibers of the anatomic lung tissue possess both expansibility and a contractile force; either of these properties might be injured separately or both might be lost at the same time. In atelectasis the expansibility of the pulmonary tissue is hindered whereas the contractibility is intact, hence the tendency of such tissue to remain collapsed. It is at once apparent that the degree and permanency of the atelectasis depends a great deal on the cause which occasions this condition; it may result from simple attenuation of the expansibility of certain portions of the lung tissue because of disuse or from various pathologic changes which have taken place in this or that area of the lung tissue. Thus atelectasis may be merely functional, that is, no pathologic changes ensued in the alveolar structure but they became deflated simply because they had not been used, such as the base of the lung of shallow breathers; such alveoli can be separated by deep breathing and their expansible force returns to physiologic limit after a repeated deep inspiratory exercise. The atelectasis resulting from pathologic alteration in the pulmonary tissue, such as edema or infiltration which actually injure the expansibility of the elastic fibers, become more permanent, the walls of the alveoli are rough, moist, and stuck together, and it requires greater inspiratory force to inflate such alveoli. Consequently, the râles produced in pathologic atelectasis will differ from the râles produced in the functional atelectasis, and can therefore be used as a differential sign.

The musical quality of the crepitant and subcrepitant is described as the sound made by rolling a lock of hair between the fingers held close to the ear, or by throwing a pinch of salt upon a hot stove. This description could be tolerably applied to the râles heard over functional atelectasis, but the râles elicited over pathologically atelectatic tissues have a more sticky quality and could be best imitated by placing two wet sheets of paper with rough surfaces upon one another, and, holding them near the chest piece of the stethoscope, separating them forcibly. This acoustic distinction between the râles has not as yet been stressed in the medical literature, though it is of utmost clinical value, particularly in tuberculosis.

From careful roentgenoscopy, roentgenography, and stereo-roentgenology of numerous cases with various parenchymatous râles, I have gained the following impressions:

(a) The crackling parenchymatous râle is heard at the end of deep inspiration and might disappear after a few respiratory exercises. Such atelectatic areas appear somewhat hazy on roentgenoscopy, but they "light up" after profound breathing, which means that air was forced into the atelectatic alveoli. In cases of thoracoplasty these crackling parenchymatous râles are always elicited after deep breathing and they never disappear. Fig. 8 is a case of complete right thoracoplasty. Crackling parenchymatous râles were elicited from apex to base on deep inspiration produced unquestionably by forceful separation of certain of the compressed bronchioles and alveoli which do not function in ordinary breathing. In thoracoplasty, there is no actual loss of pulmonary tissue, but the entire lung is reduced in volume and compressed, that is, atelectatic due to an extrinsic cause. Consequently, when air is drawn in forcibly, certain of these alveoli inflate partly and give rise to these râles. In case of fluid in the chest, which compresses the lungs completely no râles are heard, but after aspiration crackling parenchymatous râles are elicited on deep inspiration for a few days.

(b) The sticky parenchymatous râles, like those produced by the sudden separation of two rough wet sheets of paper, are seldom elicited on inspiration alone, even on deep inspiration. They can be provoked after cough followed by a deep inspiration in which case they might be heard throughout the inspiratory phase. The pulmonary area over which the posttussic râles are obtained is always hazy on roentgenologic examination; it has a ground-glass appearance, and fails to "light up" under the fluoroscope even on the most profound inspiration, only cough might render such area somewhat brighter roentgenoscopically. On the roentgenogram the haziness resembles that of an expiratory Roentgen ray plate.

The mechanism of these râles might be explained as follows: the edematous or infiltrated alveoli lost a great deal of their expansile property, and their moist and rough surfaces stick together, becoming totally deflated, that even the air of profound inspiration is not enough to separate these alveolar walls; however, on cough, when intrapulmonary pressure is greatly increased, it makes it possible for the following inrushing air to separate these agglutinated alveoli which imparts that peculiar sticky characteristic to these râles.

Excluding acute pulmonary affection, such râles are strongly indicative of pulmonary tuberculosis, which though it might not manifest itself constitutionally, is potential in developing into clinical activity. In studying serial Roentgen ray plates in cases of pulmonary tuberculosis which apparently healed by resolution, and no trace of infiltration could be seen any more on the roentgenograms, I observed that those cases, in which the posttussic râles just described persisted over the affected areas, were subject to

flare-ups, and such areas were not "lit up" properly under the fluoroscope. The disappearance of the posttussic râles in cases of pulmonary tuberculosis healed either by fibrosis or by resolution is of good prognosis. Such posttussic râles might also be heard at the base of either lung in postpneumonic cases, and could not be differentiated from pulmonary tuberculosis except by history and their limitation to the base.

(c) Sticky subcrepitant râles heard on ordinary inspiration over an isolated area of the pulmonic field are strongly suggestive of small cavitation. Such areas show up on the roentgenoscope and roentgenogram either as a honey-comb area, or as a definite small cavity with even small fluid level (see section on pulmonary cavitation). Fig. 3 is very illustrative in this respect; feeble bronchovesicular breathing and sticky inspiratory râles were heard over about 2 inches at the fourth interspace of the left chest and a definite cavity of about the same size is seen on roentgenogram, and in the second space of the same side there is a honey-combed area with a small cavity which revealed itself on physical examination by a harsh inspiratory sound and moist râles on ordinary breathing. When the cavity becomes larger, with a noticeable fluid level, the râles assume a stirring and gurgling quality.

It is thus obvious that the diagnostic significance of these parenchymatous or subcrepitant râles is determined first by their particular musical quality which is rather difficult to define exactly until one becomes accustomed and well acquainted with their sound; second, the time of occurrence of these râles in the respiratory cycle, on ordinary breathing, on deep breathing or only after cough is of great importance.

The modification of the respiratory sound has no relation to the characteristics of the râles, any shade of breathing might be obtained with any of these râles. But when bronchial breathing is heard without any râles, pleural effusion is to be diagnosed. Dry râles, sonorous or sibilant, are produced in the bronchi and neither roentgenoscopy nor roentgenography reveals any changes in the pulmonary field, if no parenchymatous lesion coexists.

Compensatory Emphysema. In discussing the circulatory changes which take place in cases of artificial pneumothorax¹⁵ I drew attention to the sharp distinction in the mechanism and alterations of hypertrophic and compensatory emphysema. In hypertrophic emphysema the pulmonary capillaries are compressed because of overdistention of the alveoli, the elastic tissue of which has lost a great deal of its contractile power, the residual air is increased, and the ventilation of the lungs is very poor. Such lungs appear over-aërated on the roentgenogram, with blurring of the lung markings, and roentgenoscopically the lungs seem overilluminated even on expiration, which shows an expiratory overdistention. This is the reason why the expiratory breath sound of an emphysema is feeble and prolonged.

In compensatory emphysema, on the contrary, the distention of the alveoli is a result of the engorgement and dilatation of the capillaries surrounding the air sacs, and the elastic tissue of such a vicariously hypertrophied lung retains both its expansile and contractile power; consequently the lung ventilation is more effective. Roentgenographically the lung markings of such lungs are accentuated, and roentgenoscopically the lungs are seen to expand and contract fully causing a marked difference between the illumination of the pulmonic field in inspiration and expiration. This explains why the breath sounds of such a lung are exaggerated and puerile in character. Fig. 8 shows a vicariously emphysematous left lung.

The gradual development of compensatory emphysema and the modification in the breath sounds following such changes can be best studied in cases of artificial pneumothorax. Roentgenograms taken shortly after the induction of pneumothorax show a somewhat hazy appearance of the contralateral lung with marked accentuation of the lung markings. This is due to the engorgement of the pulmonary bloodvessels as a result of a greater amount of blood being driven through the same capillary bed per unit of time. The alveoli of the lung do not become over distended, until a few weeks later. Percussion at this time usually reveals slight diminution in resonance over this lung and breath sounds are not changed. Gradually the breath sounds over the lung grows harsher and becomes exaggerated or puerile in character. At this time the expansion and contraction of the lung assumes a wider range, as can be shown roentgenoscopically.

Conclusions. An endeavor has been made to show that roentgenology could be used to great advantage in the investigation of the mechanism of physical signs of the chest and in evaluating their diagnostic and prognostic significance. The application of this investigational method to the study of the physical signs of pulmonary cavities, pneumothorax, certain râles, and so forth, assisted a great deal in elucidating the mechanism of many of these signs and brought about a revision in their diagnostic interpretation:

1. About 50 per cent of the pulmonary cavities are silent as to the classical signs of cavitation; of these few are absolutely mute, not revealing themselves by any adventitious sounds, but most of them can be detected by congeries of signs, such as modified breath sounds with moist inspiratory râles heard over an isolated area of the lungs.

2. The presence of amphoric breathing indicates a pleural-visceral opening. As soon as the opening closes the amphoric breathing disappears and the lung begins to reexpand, as can be watched roentgenoscopically. The varying physical signs of pneumothorax in the same side of the chest are determined by the modified pneumodynamics and the localization of gas in that pleural cavity.

3. (a) Subcrepitant crackling râles heard over an area on deep inspiration are due to functional atelectasis. (b) Subcrepitant

sticky râles which are elicited only after cough are due to edema or infiltration of the alveolar walls; these areas fail to "light up" under the fluoroscope on inspiration. (c) Moist râles heard on ordinary inspiration over a limited area of the pulmonic field with modified breathing are strongly suggestive of small cavitation.

4. A peculiar friction rub heard over the sternum anteriorly or over the thoracic vertebra posteriorly in cases of pneumothorax is due to the pendulum-like movement of a labile mediastinum, moving back and forth with the respiratory cycle.

5. The marked distention and contraction of the vicariously dilated lung in cases of compensatory emphysema causes the breath sound to become puerile or exaggerated in character.

Roentgenoscopy, roentgenography, and stereoroentgenography could no doubt, be used advantageously in the study of the mechanism and physical signs of many other chest abnormalities.

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ENCEPHALOGRAPHY.

LUMBAR PUNCTURE AND TREPHINE METHODS.

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FOR the purpose of this article the term encephalography is sufficient for the discussion of analysis of the brain by the injection of air either through a lumbar puncture or a small trephine, or by the combined use of both methods in connection with Roentgen ray films.

Bingel,⁷ Weigeldt,⁸ Gabriel,¹² Denk,¹⁰ Schoot and Eitel,²⁹ Jungling,⁹ Schuller,¹¹ Liberson,⁵ and others have reported numerous cases where lumbar puncture and injection of air has been employed successfully for diagnosis and localization in various types of brain lesions, but the procedure has been accompanied by frequent profound reactions, such as pain in the head, severe headache, vomiting and diarrhea, or by collapse and shock during and following the test under local anesthesia. Also some fatalities have been reported.

The trephine method of air injection as developed by Dandy¹ under the term "Ventriculography," and also employed by Schuller,¹¹ Weigeldt,⁸ Herrmann,²⁵ Davenport,²¹ Elsberg,³ Adson,¹⁶ McConnell,¹⁸ Grant,⁴ Locke,⁶ and various other writers, is employed almost exclusively in this country, and to a great extent this method has supplanted lumbar puncture in foreign countries notwithstanding a mortality of 5 to 10 per cent from the procedure. However, the trephine method is used by most investigators only in a class of cases where practically 100 per cent mortality occurs within a brief period unless relief can be procured.

Although, the extreme discomfort from the lumbar puncture method as usually made, and its limited field in well developed and in terminal brain lesions have greatly restricted its use, yet this form of encephalography when employed under proper conditions becomes an indispensable factor in the investigation of early tumor suspects and in all forms of brain disturbances which cannot be satisfactorily determined by the usual methods of diagnosis. The lumbar puncture method is less dangerous than the trephine method and has a wide range of usefulness, but neither test should be used to the exclusion of the other, and occasionally both methods are necessary.

The Lumbar Puncture Method. The lumbar puncture method can be utilized in almost any patient with comparative safety, except in those with tumors of the posterior fossa or with extensive communicating type of hydrocephalus. Correct interpretation of

the usual Roentgen ray films along with a proper understanding of cerebellar disturbances and of the Bárány vestibular tests will eliminate the danger of tumor, while the presence of extensive hydrocephalus should be detected before a very harmful amount of air has replaced the fluid withdrawn during the test, otherwise, the fluid should be reinjected by the trephine method. As a rule, the lumbar puncture test should not be employed when any brain tumor is strongly suspected or known to be present, yet at times it is of value in supratentorial tumors. Occasionally, the lumbar puncture test is difficult to interpret, especially if an excess of air has not been injected. In about 15 per cent of the tests by lumbar puncture, the trephine method is also necessary to further clarify the situation due to impervious third ventricle, or to blocked ventricles from tumor, from luetic, inflammatory and traumatic lesions, or from abscess.

The lumbar puncture method under local anesthesia is almost prohibited, yet, when it is made under ether anesthesia and the patient is placed in the upright sitting posture, there is but little likelihood of immediate or late disturbance beyond moderate headaches in some patients and slight discomfort for two to five days. The upright posture is necessary in order to drain and fill the lateral ventricles and sulci to the best advantage. The experienced operator usually knows when the ventricles are being drained and how much fluid to remove. At times all fluid must be drained and replaced by an equal or excess amount of air. In adults at least 60 to 80 cc. should be removed, as certain conditions reduce the amount of fluid below the average of 120 cc. When less than 80 to 90 cc. only can be obtained in adults, either the ventricles are not being drained or some abnormal condition has reduced their capacity.

The average normal spinal fluid pressure in adults in the upright position under ether is about 35 mm. mercury. Considerably more air than fluid removed can be injected with safety in the usual patient. At least 10 per cent more air than fluid is desirable for good films and for therapeutic purposes to which reference will be made later. A small needle with two or three inlets, a small rubber tube, and a 10 cc. or larger glass syringe is all the equipment necessary to make the test.

Frequently the lumbar puncture test is made in my office and the patient is taken home immediately or soon after the Roentgen ray films have been completed. It is not unusual for them to be taken 50 to 100 miles in auto or train the same or succeeding day of the test. In no case has a severe reaction occurred under ether and the headaches are of milder type than when done under local anesthesia. The headaches may persist a few days, but often the patient is up and around the next day. At times the usual "lumbar puncture

ENCEPHALOGRAPHY BY LUMBAR PUNCTURE AND TREPHINE METHODS.

No.		Age.	Complaint.	Dura- tion.	Procedure.	Findings.	Diagnosis.	Remarks.
1	19	45	Headaches	4 yrs.	Lumbar puncture	Small ventricles	Psychosis	Fat, not a well child.
2	45		Headaches	1 yr.	Lumbar puncture and trephine	Trace of air in ventricles	Luetic	Recovered under treatment.
3	30		Headaches	8 yrs.	Lumbar puncture	Trace of air in ventricles	Tumor left	Meningioma left parietal region.
4	7		Headaches	5 yrs.	Lumbar puncture	Normal	Tumor	Both lateral ventricles involved.
5	26		Headaches	6 yrs.	Lumbar puncture and trephine	Normal	Psychosis	Committed suicide recently.
6	28		Headaches	7 mos.	Trephine	Left ventricle shallow	Meningeal	Improved after air test.
7	12		Headaches	2 yrs.	Trephine	Normal	Head injury	No recurrence headaches after test.
8	24		Headaches only	4 yrs.	Lumbar puncture	Moderate hydrocephalus	Meningeal	No recitation.
9	26		Headaches	3 mos.	Lumbar puncture	Normal	Head injury	Operation.
10	26		Headaches and convulsions	12 yrs.	Lumbar puncture	Left ventricle shallow	Meningeal	No headaches after air test, 1 yr.
11	24		Headaches and convulsions	4 yrs.	Lumbar puncture	Normal	Cerebellar	No headaches after air test, trephine indicated.
12	18		Headaches and vertigo	3 mos.	Lumbar puncture	Normal	Tumor	No headache open, trephine autopsy.
13	30		Headaches and choked disks	12 yrs.	Lumbar puncture	Lateral ventricle	Meningeal	No ventricle open, trephine.
14	28		Headaches and choked disks	4 yrs.	Lumbar puncture	Large left ventricle	Meningeal	Third septum lucidum, operation.
15	15		Headaches and choked disks	8 mos.	Lumbar puncture	Few drops only	Meningeal	Tumor septum lucidum, operation.
16	16		Headaches and choked disks	8 mos.	Trephine	Normal	Tumor suspected	Tumor top of head; operation.
17	17		Headaches and choked disks	8 mos.	Trephine	Ventricles blocked	Tumor foramen Monro	Recovered under rest.
18	35		Headaches and choked disks	2 wks.	Lumbar puncture	Hydrocephalus	Block abscess	Recovered under rest, recovered.
19	12		Headaches and choked disks	2 yrs.	Trephine	Left anterior horn obliterated	Brain abscess	Injected Zenker's fluid, recovered.
20	40		Headaches and choked disks	5 mos.	Trephine	Right anterior horn obliterated	Functional	Operation and autopsy.
21	40		Headaches and choked disks	1 yr.	Trephine	Right ventricle blocked	Suprasellar cyst	Operation refused.
22	40		Sick, coma	6 mos.	Trephine	Cystic fluid	Tumor third ventricle	Operation; recovery.
23	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Tumor frontal lobe	Operation; death 1 yr.
24	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess frontal lobe	Operation; indicated.
25	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Parietal tumor	Trephine indicated.
26	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Tumor frontal lobe	Death, 2 weeks later.
27	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Encephalitis	Operation; death later.
28	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	Autopsy.
29	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
30	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few hours.
31	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
32	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
33	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
34	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
35	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
36	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
37	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
38	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
39	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
40	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
41	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
42	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
43	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
44	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
45	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
46	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
47	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
48	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
49	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
50	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
51	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
52	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
53	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
54	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
55	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
56	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
57	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
58	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
59	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
60	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
61	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
62	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
63	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
64	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
65	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
66	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
67	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
68	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
69	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
70	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
71	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
72	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
73	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
74	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
75	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
76	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
77	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
78	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
79	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
80	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
81	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
82	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
83	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
84	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
85	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
86	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
87	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
88	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
89	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
90	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
91	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
92	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
93	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
94	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
95	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
96	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
97	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
98	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
99	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.
100	40		Sick, coma	4 mos.	Trephine	Right ventricle blocked	Abscess, frontal lobe	No operation, died in few days.

30	Headaches, hiccoughs	6 mos.	Trephine	Moderate hydrocephalus	Cerebellar tumor	Operation, tuberculoma.
31	Headaches, Jacksonian con- vulsions	6 mos.	Lumbar puncture	Normal	Cortex tumor	Operation, pea size near arm center.
32	Drum states	6 yrs.	Lumbar puncture	Left ventricle obliterated	Deep tumor?	Head injury at 9 yrs.
33	Spasm neck	2 yrs.	Lumbar puncture	Normal	Psychic?	All treatment ineffective.
34	Convulsions only	3 yrs.	Lumbar puncture	Trace of air in ventricles	Tumor?	Both ventricles, luetic. (?)
35	Convulsions	4 yrs.	Trephine	Small normal	?	Course like multiple sclerosis, improved.
36	Convulsions	12 yrs.	Trephine	Left ventricle large	Head injury	Test through old wound.
37	Convulsions	4 yrs.	Lumbar puncture	Hydrocephalus	Early meningitis	All ventricles enlarged.
38	Spastic convulsions	2 yrs.	Lumbar puncture	Hydrocephalus	Birth injury	Head not enlarged.
39	Convulsions	10 yrs.	Lumbar puncture	Normal	Congenital	Twin 2½ lbs, sick baby convulsions.
40	Convulsions	4 yrs.	Lumbar puncture	Normal	Meningeal	"Cried much when a baby."
41	Convulsions	10 yrs.	Lumbar puncture	Left ventricle large	Atrophy	"Sick baby."
42	Convulsions	8 yrs.	Lumbar puncture	Normal	Birth or congenital	Was a sick baby.
43	Convulsions	8 mos.	Trephine and lumbar puncture	Absence of sulci, left	Chronic meningitis	Secondary to mastoiditis, recovered.
44	Convulsions	4 yrs.	Lumbar puncture	Normal	Psychic?	Spasms, sterno mastoids.
45	Convulsions	1 yr.	Lumbar puncture	Left ventricle blocked	Tumor left	Operation.
46	Convulsions	2 yrs.	Lumbar puncture	Hydrocephalus	Meningitis at 2 yrs.	Head not enlarged.
47	Convulsions right	8 yrs.	Lumbar puncture	Vs. normal or large	Birth injury	"Was a blue baby."
48	Hydrocephalus	2 mos.	Trephine	Block fourth ventricle	Congenital	All ventricles enlarged.
49	Convulsions, vertigo	4 yrs.	Lumbar puncture	Normal	Luetic	Recovered by treatment.
50	Convulsions, blind	15 yrs.	Lumbar puncture	Normal ventricles	Congenital	Blind for years.
51	Convulsions, aphasia	4 yrs.	Lumbar puncture	Left ventricle large	Luetic	Recovered under treatment.
52	Choked disks only	2 mos.	Trephine	Left anterior horn obliterated	Tumor left	Operation, glioma left temporal region, recovered.
53	Impaired mentality convul- sions, 1 yr.	5 yrs.	Lumbar puncture	Trace of air in ventricles	Tumor?	Trephine indicated, died later.
54	Right paresis	1 yr.	Lumbar puncture	Normal	Luetic?	3 miscarriages.
55	Impaired mentality	2 yrs.	Lumbar puncture	Normal ventricles	Congenital	Brother 3 yrs. old same trouble.
56	Impaired mentality	7 yrs.	Lumbar puncture	Normal ventricles	Meningitis at 8 yrs.	Convulsions when 8 yrs. old.
57	Petit mal, convulsions	3 yrs.	Lumbar puncture	Left ventricle large	Atrophy	Meningitis when young.
58	Petit mal, convulsions	5 yrs.	Lumbar puncture	Left ventricle shallow	Tumor	Has perverted taste.
59	Petit mal, convulsions	5 yrs.	Lumbar puncture and trephine	Block lateral ventricles	Injury foramen Monro	Head injury.
60	Petit mal, convulsions	4 yrs.	Lumbar puncture	Normal	Congenital	(Sister not right) improved by test.
61	Petit mal, convulsions	6 yrs.	Lumbar puncture	Third ventricle only injected	Tumor	Typhoid at 4 yrs., petit mal soon after.
62	Neuralgia arm	4 yrs.	Lumbar puncture	Normal ventricles	Functional	Cortex lesion possible.
63	Neuralgia ear	2 yrs.	Lumbar puncture	Normal	Ninth nerve	Craniospasm, one side.

headaches" occur from seepage of the fluid into the lumbar tissues. In one case of this nature where the intracranial pressure was increased the headaches persisted for three weeks. The headaches from the air test result from irritation and expansion of the meninges which also produce the shock and other reactions under local anesthesia. These headaches are readily controlled by opiates, if necessary.

The Trephine Method. As stated, the trephine method is employed where some grave condition, as tumor, abscess, or hydrocephalus is present or is strongly suspected, and to verify or further analyze certain conditions as revealed by the lumbar puncture test where the ventricles are partially or totally impervious by that route. This method is a graver procedure than the lumbar puncture method under ether, and must be made in a hospital where emergencies can be met.

Various locations for the trephine have been used, but the lateral entrance, according to Keen, has been more satisfactory than other points since lateral displacement of the ventricles by tumors, abscess, and so forth, does not interfere materially with this place of entrance. Slightly more difficulty may be experienced in draining the third ventricle from this angle than from the occipital region and care must be taken not to enter the lateral sinus as I have done on two occasions although without any serious consequence. The amount of fluid to remove depends entirely on conditions. At times 10 to 20 cc. of air is sufficient, while at other times 50 to 100 cc. or more of air is necessary for interpretation of the films. Slightly more air should be injected than fluid withdrawn. In normal cases and where hydrocephalus does not exist, the air will be absorbed through the same channels as the fluid and will do no harm. Where more than moderate hydrocephalus does exist the air should be expelled several hours later by repeated puncture. In extreme cases it is advisable to replace the air by the original fluid or by a neutral Ringer's fluid. Either local or general anesthesia may be used in making this test on children or adults, as severe reactions are infrequent.

Encephalography, as considered in this article, may be employed to great advantage in any brain disturbance where a diagnosis is doubtful. It is valuable in revealing a gross normal condition of the brain as well as revealing abnormalities of various kinds; consequently it is of inestimable value in the investigation of petit mal and in convulsions of unknown origin, in certain forms of chronic headaches, in occasional cases of mental impairment, in certain head injuries, and in other motor and sensory disturbances. By employing the method of choice in these vague cases there are relatively but few of them that cannot be satisfactorily explained, thus eliminating long intervals of observation of many patients with or without tumor of the brain, and other conditions are much

better understood and treated to greater advantage. Other writers^{7,11,9,5} also have observed that the performance of this test has a definite therapeutic value in certain forms of meningeal and ventricular disturbances.

The following tabulated record of cases constitute a group of private patients on whom the tests were made during a period of eighteen months:

Comments. Sixty-three cases are reported where the lumbar puncture and trephine tests were employed.

Of 40 lumbar puncture air tests: 19 showed normal findings; 21 abnormal findings; 7 were indefinite and the trephine test was indicated to complete the examination; 1 lumbar puncture patient, aged two years, with hydrocephalus died ten days after the test.

Of 23 primary trephine air tests: 4 showed normal findings; 19 showed abnormal findings; 1 trephine patient in coma died 2 hours later; 2 trephine patients with cerebellar tumors and choked disks died one week after operation. Possibly death was hastened by retained air as drainage of the ventricles could not be reestablished, and the air was not removed, or replaced by fluid.

Chief Complaints and Pathology. Twenty-three headache cases were associated with brain tumors; 24 convulsive and petit mal cases were of a chronic type; 3 chronic brain abscess cases were encountered; 24 brain tumors were found, according to tests, operations and autopsies; 24 cases were classified under birth injury, congenital and meningitic origin; 13 cases were classified as functional psychosis, neuralgia, impaired mentality, encephalitis and luetic.

Results: 3 patients with chronic headaches of a very severe nature were relieved of the disturbance without further treatment after the air test. Several other disturbances improved without treatment and one patient (No. 35) apparently has recovered; 15 patients recovered or were markedly improved by appropriate operations and treatment; 11 patients classified as tumor suspects, neuralgia, functional, and psychosis cases were considered as possible future recoveries; 37 patients were classified as hopeless for improvement or have died.

With the exception of 4 or 5 patients, the disturbances in this group of cases were of a chronic nature. Virtually all of the patients had been examined numerous times by competent physicians, and as a rule, the diagnosis of epilepsy and migraine had been made. The majority of these patients presented no other neurological symptoms than headaches, petit mal, or convulsions, and associated choked disks in the late tumor cases. The usual laboratory reports, including the blood and spinal fluid had been negative in these patients with the exception of two with brain abscess and three or four with tumors. Numerous patients were unconscious and in

the terminal stage of brain tumor at the time of the examination. From the information gained by encephalography in connection with the history and clinical data, a satisfactory working diagnosis was obtained in practically all cases. In addition to the tabulated report, attention is directed to a brief discussion of special features in certain cases.

CASE III.—A woman, aged thirty-six years, had severe headaches without other disturbances for eight years. The lumbar puncture air test revealed both lateral ventricles to be almost obliterated by a tumor in the left parietal region (meningioma shadow on left side).

CASE XII.—A girl, aged eighteen years, had four or five convulsions with moderate headaches during eight months time, otherwise she was in good health. The lumbar puncture test revealed the third ventricle to be open while each lateral ventricle was blocked. The trephine test should have been made on both sides as she probably had a tumor (foramen Monroe).

CASE XXXVIII.—A child, aged two years, had been somewhat spastic all its life and developed convulsions during the last month before examination. The head was not unusually large. The lumbar puncture test with the removal of 150 cc. of clear fluid revealed marked communicating hydrocephalus. The air was not replaced by fluid as should have been done in this case and the patient died in ten days.

CASE LXIII.—A child, aged four years, had neuralgia in the right ear region for two years which at times could be controlled only with chloroform. The usual Roentgen ray films revealed increased intracranial pressure. The lumbar puncture air test revealed a normal gross condition of the brain. A decompression for one sided craniostenosis relieved her materially of the pain which no doubt was of glossopharyngeal origin.

CASE VII.—A girl, aged twelve years, was thrown from a horse and injured two years before examination. Soon after the accident she suffered numerous times daily with intense pain in the head. The trephine air test revealed one ventricle to be somewhat smaller than the other which appeared to be normal. Eighteen months after the air test she had not had any recurrence of the pain.

CASE VIII.—A woman, aged twenty-four years, had headaches at intervals during four years and had been confined to her bed for four months at the time of the examination. There was no evidence of organic lesion of the nervous system and the pain was not relieved by cocainizing the nasal ganglion. The lumbar puncture air test with the pressure raised considerably above normal revealed normal ventricles and one week after the test she was entirely relieved of the headaches without recurrence at the end of one year.

CASE XVI.—A boy, aged twelve years, had headaches for five months and choked disks for two months. The usual Roentgen ray films revealed high intracranial pressure but no calcified areas. The trephine air test on each side three months later revealed there was no connection between the two lateral ventricles. A diagnosis of suprasellar tumor was made. Puncture through a right side decompression with drainage of about 30 cc. of yellow fluid which clotted, was followed by irrigation of the cyst with distilled water and injection of 20 cc. Zenker's fluid which was removed by

irrigation. The patient made a complete recovery with the exception of optic atrophy which occurred before any operative measures were permitted by the parents.

CASE XV.—A girl, aged twenty-eight years, developed vertiginous attacks, agonizing occipital pain, disturbance in vision, marked ataxia, and paresthesia of the right side. After two years of increasing disturbance the lumbar puncture air test revealed a normal gross condition of the brain. She was relieved of the disturbances and resumed her work after two months' rest treatment.

CASE XIX.—A boy, aged twelve years, developed meningitis, osteitis, and choked disks during the four months before the examination. No localizing symptoms were present. The trephine air test revealed absence of the anterior portion of the right lateral ventricle. A large abscess was drained with no recurrence of trouble one year later.

CASE IX.—A man, aged twenty-four years, had severe headaches for three months without other symptoms. The trephine air test revealed moderate and symmetrical enlargement of the lateral ventricles. The vestibular tests revealed absence of past pointing of the right hand to the left. A cerebellar operation disclosed a small glioma near the mid line on the right side.

CASE XLIII.—A child, aged four years, had 8 to 16 hard convulsions daily, at times without other symptoms for eight months. The lumbar puncture air test revealed absence of sulci over the left temporo-parietal region which directed attention to a latent mastoiditis with a normal middle ear. The mastoid operation with a decompression and punctures relieved her permanently of the convulsions.

CASE LIX.—A man, aged twenty-four years, had many dream-like spells and convulsions during four years' time. The lumbar puncture air test revealed the right lateral ventricle only to be open. The trephine air test on the left side revealed a large ventricle from blocking at the foramen of Monro, no doubt the result of an old head injury.

CASE X.—A woman, aged twenty-six years, suffered with headaches for twelve years which required opiates and she was confined to her bed much of the time. There was no evidence of nasal disease and no symptoms of organic brain trouble. The lumbar puncture air test under ether revealed a normal gross condition of the brain. One year later she had had no recurrence of headaches following the air test.

CASE XXXI.—A girl, aged nineteen years, had convulsions which began in the right arm and face during a period of five months before examination. She had headaches and much disturbance of vision but no fundus trouble. The lumbar puncture air test revealed normal ventricles which was quite conclusive that she had a cortex disturbance. A small tumor was removed at operation with apparently permanent relief of the complaints.

CASE LXI.—A girl, aged ten years, had petit mal and convulsions for six years. The lumbar puncture air test revealed the third ventricle only to be open. The trephine air test was indicated on each side.

CASE XXVI.—A woman, aged forty-five years, had headaches for one year followed by choked disks and coma without any localizing symptom.



FIG. 1.—Case 5: Normal ventricles in a patient previously considered to be a “brain tumor suspect.” (Lumbar puncture.)

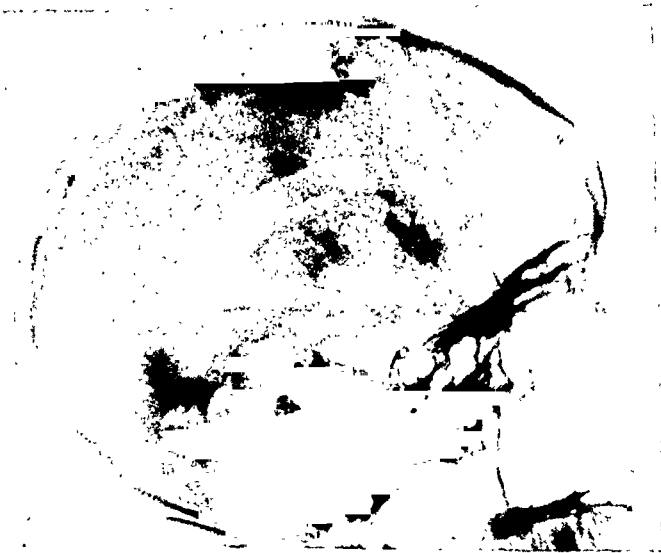


FIG. 2.—Case 35: Normal lateral ventricles in a patient who had convulsions from an unknown origin. (Multiple sclerosis?) (Trephine.)



FIG. 3.—Case 9: Trephine. Cerebellar tumor. Headaches only symptom.

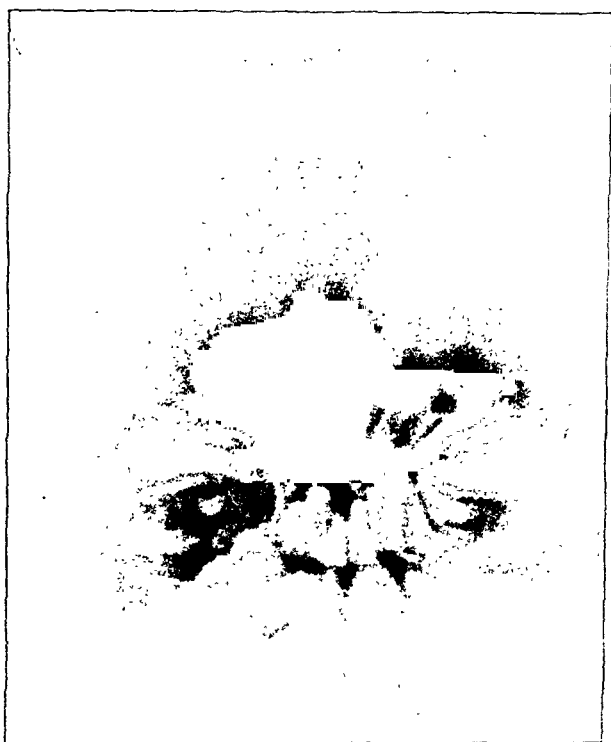


FIG. 4.—Case 23: Right frontal lobe abscess. Both anterior horns are displaced to the left. (anteroposterior view). (Trephine.)



FIG. 5.—Case 37: Lumbar puncture. Communicating type of hydrocephalus. Boy, aged seven years; convulsions, four years.

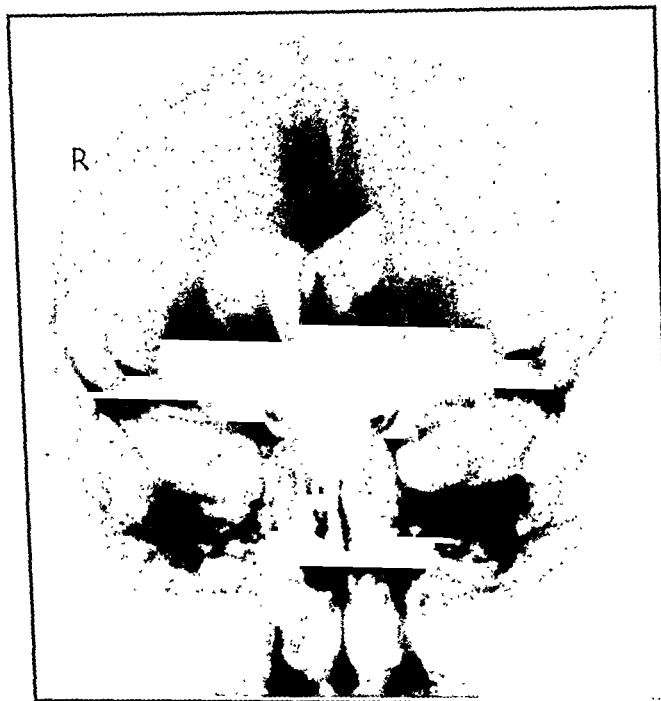


FIG. 6.—Case 52: Trephine. Choked disks only symptom. Tumor left temporo-frontal region. Operation; recovery.

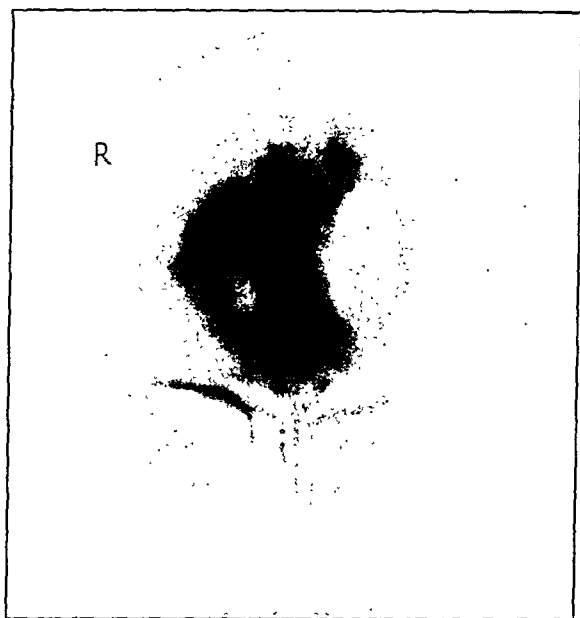


FIG. 7.—Case 16: Trephine each side. No communication between lateral ventricles. Suprasellar cyst; no calcified area. Operation; recovery.

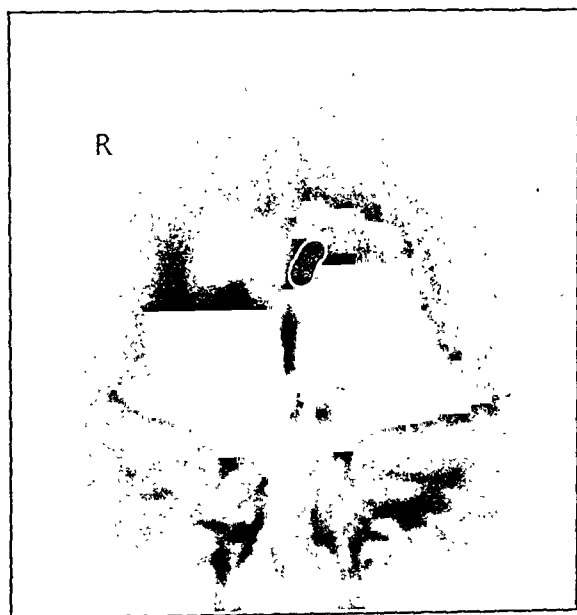


FIG. 8.—Case 23: Lumbar puncture. Left ventricle admits only trace of air. Tumor left side. Convulsions and perverted taste.

There was insufficient space for injection of air into the left ventricle by the trephine test, and not more than a dram of fluid was present in the right ventricle. The attempt to inject air into the right ventricle was unsatisfactory and the patient died two hours later; death possibly was hastened by the presence of a small amount of air in the brain tissue. The injection of air in this class of patients and in those with tumors involving the brain stem is accompanied with considerable danger and every precaution should be taken when making the test in these patients.

CASE LI.—A man, aged forty-four years, with a negative history and laboratory reports had convulsions and aphasia for four years. The trephine air test revealed some enlargement of the left ventricle. He made a complete recovery under intensive luetic treatment.

Conclusions. From an analysis of 63 patients on whom encephalography was practiced it is concluded that:

1. In addition to the restricted group of patients with brain tumor, hydrocephalus, or abscess where the trephine method is employed for diagnosis and localization, encephalography, as considered in this paper, is indispensable in the investigation of many patients troubled with headaches, petit mal, convulsions, impaired mentality, and other vague neurological complaints of a more or less chronic, or of a recurring nature.

2. Encephalography by the lumbar puncture method *under ether anesthesia*, with the patient in the upright sitting position, practically is devoid of the serious reactions met with when made under local anesthesia and is not more dangerous, than many other useful procedures such as tonsillectomy and appendectomy, except in patients with well developed brain tumors, with abscess, or with communicating type of hydrocephalus.

3. Either distention of the membranes, or reaction from the presence of air in this form of encephalography, is beneficial in certain types of headaches, and possibly in other conditions.

4. Encephalography by these methods requires a thorough working knowledge of neurology, as well as neuro-surgical training and Roentgen ray interpretation.

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STUDIES ON LEUKEMIA.

I. CONCERNING THE FRAGILITY OF THE WHITE BLOOD CELLS.

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WORKING on the leukemia problem my attention turned to a theory first emphasized by Wolff,¹ according to which the tissue hyperplasia together with the enormous cell production would present only the secondary consequence of the previous extensive cell destruction. From such an aspect it is only a regenerative effort, a defense by the organism against the unknown factor, the nature of which would be perhaps that of a toxin originating in the organism itself, perhaps in invading parasites. This toxin, reacting upon the corresponding white blood corpuscles, causes their destruction by leukolysis in the serologic sense. Thus the primary cause of the disease would be looked for in these leukolysins.

The theory is supported, however, by no argument based on experiments and the whole assumption is grounded upon morphologic changes of degenerative character first described by Gumprecht.² The main symptoms of this cell degeneration are: The protoplasm disappears, the nuclei become flattened with uneven outlines, with loose structure and often with vacuoles, the chromatin grows less and less, finally disappearing entirely.

This observation of morphologic character would be supported by the fact frequently noted that the quantity of the uric acid in the blood as well as in the urine is remarkably increased. And this increase in uric acid is attributed to the white blood cell destruction. This fact, however, proves the increased cell destruction only, giving no evidence of its priority.

With regard to the fact that one is not justified in drawing such far-reaching conclusions from morphologic changes only, even of the most important nature, it was considered not superfluous to look for such evidences in a significant number of leukemic patients.

The investigations conducted in the last two years are as follows:

I. **Experiments in Vitro.** In these experiments the endeavor was made to imitate, so far as possible, the process in the human organism. For this reason I let the fresh serum of untreated leukemic patients react upon the white blood cells of healthy persons of the same sex.

For the isolation of the white blood corpuscles the method

I elaborated some while ago was of use.³ After washing in Locke's solution, the leukocytes were suspended in leukemic serum. Experience will teach the density wanted and after some practise the right density is easily secured. I usually suspended the leukocytes isolated from 10 cc. of blood in 2 to 3 cc. of serum. The leukocytes suspended in this way were placed in small agglutinating tubes in the incubator at 37° C. and were counted at intervals. To prevent sedimentation, the suspension is to be mixed with a capillary pipet by alternate aspiration and expulsion about every two hours. Avoid air bubbles if possible! At the beginning I imagined that the frequently repeated mixing represented such a vigorous mechanical insult that the white blood corpuscles would be injured. But numerous experiments showed that the leukocytes of healthy persons did not suffer any mentionable harm suspended in the serum or plasma of another healthy person of the same sex. In the suspension there were nearly as many leukocytes after twenty-four hours incubation as at the beginning of the experiment.

The white blood cells were counted at first every two hours, later every four hours. As usual in the counting of leukocytes the suspension was sucked up to the upper mark on the tube and was diluted by Locke's solution stained with gentian violet. After thorough mixing the counting was performed in a Buerker chamber (Zeiss). The cells were counted in five big squares (that is in 5 by 16 smaller squares) and as average there was given the cell number according to *one* big square, regardless of the dilution which seemed quite superfluous.

Altogether there were undertaken 30 experiments under physiologic circumstances: 17 in the serum and 13 in the plasma.

In the serum the white blood cells of healthy persons showed a decrease of between 12.7 and 17.9 per cent in twenty-four hours, giving 15.3 per cent as an average. In the plasma the decrease varied between 13.4 and 19.1 per cent, averaging 16.2 per cent.

Apparently the decrease is scarcely of importance. The leukocytes are mostly intact, the nucleus is well stained, the protoplasm is preserved; and comparatively very few cells suffered harm.

Convinced of the usefulness of the method, I turned to the examination of the problem itself.

There were examined altogether 22 cases, of which there were: chronic myelogenous leukemia, 20; acute myelogenous leukemia, 1; and chronic lymphatic leukemia, 1.

White blood cells of healthy persons suspended in leukemic serum showed a decrease of 20.2 per cent in the average, that is about 5 per cent more than in the experiments mentioned above. But one would be never justified in ascribing this slight difference to the leukolytic power of the leukemic serum, because it is generally known that in other lytic experiments—for example, hemolysis—

most cells are dissolved, if not all. It is more appropriate to look for the cause of the decrease in the changed chemistry of the leukemic serum, in its higher lipid content and perhaps in factors of physicochemical character.

One would, however, imagine that the originally existing leukolytic power of the blood perhaps is impaired with coagulation. To exclude every possibility of this sort the investigations were extended to the blood plasma, preventing coagulation by a minimal quantity of *hirudin*. The method was the same as in the experiments with serum.

The decrease was more marked here than in the serum: averaging 23.5 per cent.

One would never be justified in considering this slight difference as very significant, especially as it scarcely goes beyond the experimental error.

One might think that the hypothetic leukotoxin is an *autolysin* reacting only with the leukocytes of the person himself. A series of experiments arranged to test this point gave results of the highest interest.

Leukemic white blood corpuscles suspended in the patient's own serum presented without exception a significantly greater decrease: an average of 31.4 per cent and in their own plasma an average of 38.9 per cent. But as in other lytic experiments—for example hemolysis—the cell destruction is perfect, it became necessary to look for the cause not in the leukolytic power of the leukemic serum or plasma but rather in other circumstances. First in the leukemic white blood cells themselves, as would be suggested by Gumprecht's morphologic observations.

That leukemic white blood corpuscles have in fact a lower resistance than the ones of healthy persons is demonstrated by further experiments undertaken with the serum and plasma of healthy persons.

According to these experiments the leukemic white blood corpuscles suspended in the serum or plasma of healthy persons decreased in the same proportion as in their own serum or plasma. In the patient's own serum the diminution was of 31.4 per cent and in their own plasma 38.9 per cent, while in the serum of healthy persons 33.9 per cent and in the plasma 36 per cent.

This expressed decrease of the white blood corpuscles cannot be explained by the action of a specific autolysin occasionally present in the blood but only by the smaller resistance of the leukemic white blood cells.

It is a very interesting and peculiar circumstance that the cell decrease of healthy or leukemic white blood cells has been always better expressed in the plasma than in the serum, entirely regardless whether the plasma was of leukemic or of healthy persons.

The decrease of the various cells in twenty-four hours was as follows:

Suspension.	Decrease, per cent.
Healthy leukocytes:	
Healthy serum	15.3
Healthy plasma	16.2
Leukemic serum	20.2
Leukemic plasma	23.5
Leukemic leukocytes:	
Leukemic serum	31.4
Leukemic plasma	38.9
Healthy serum	33.9
Healthy plasma	36.0

The difference is not very much. It presents, however, such a regularity that experimental fault must be excluded and one would be perhaps not mistaken in attributing it to the different physico-chemical properties of the plasma.

During these investigations, special attention was given to the *ameboid movement* of the leukocytes as a life phenomenon. The observations lead, however, to no usable result. There were never two experiments in full agreement with each other. It happened that the leukocytes suspended in the serum or plasma of gravely sick patients moved even after twenty-four hours, while the ones suspended in the serum or plasma of entirely healthy persons stopped movement even after ten to twelve hours. Even repeated experiments with the serum or plasma of the same patient gave the most different results. For example I wish to mention only the case when the leukocytes suspended in the patient's own serum moved only for six hours, while four days later for twenty-four hours.

Apparently the ameboid movement depends in the highest degree on external circumstances. These experiments were abandoned without usable conclusions.

I endeavored also to demonstrate the hypothetic leukolysin by the help of *Bordet-Gengou's complement-fixation test*. It was thought that—if such a substance really exists—the inactivated serum reacting on the homologous antigen fixates complement, consequently in the hemolytic system added later the hemolysis stays away.

As antigen I used a 10 per cent aqueous extract of the white blood cells isolated from leukemic patients. Of the patient's inactivated serum 0.1 cc. was taken and for complement normal serum of guinea pigs was used. The hemolytic system was as usual.

A positive complement-fixation test never occurred: hemolysis was always perfect.

II. *Animal Experiments.* The supposition was that in the case of a really existing substance of leukolytic power in the leukemic

blood leukolysis would appear after the injection of leukemic blood into animals; that is the number of the white blood corpuscles would decrease.

Well-developed rabbits were used for the experiments and for the injection the fresh serum or the blood itself. To keep the blood perfectly unchanged, 3 cc. of Locke's solution were taken into a syringe and then 3 cc. of leukemic blood out of the cubital vein of the patient. Dilution with Locke's solution was in order to retard the blood coagulation. By mixing thoroughly coagulation has been always prevented.

Two experiments were undertaken with leukemic serum and two with whole blood, while two other animals were injected in the same manner by the blood or serum of healthy persons for control.

The injections caused high fever and marked leukocytosis. These well-known symptoms, however, disappeared mostly in twenty-four hours. The number of erythrocytes and the hemoglobin content showed no essential change. Apparently these experiments were of no significance.

Summary. White blood cells of healthy persons suspended in leukemic serum or plasma decreased after twenty-four hours incubation in a somewhat greater proportion than if suspended in the serum or plasma of healthy persons. The difference, however, was so slight that the assumption of a specific leukolytic action does not appear to be justified.

The decrease was more marked in the experiments undertaken with leukemic white blood cells suspended in the patient's own serum or plasma. But the diminution cannot be explained by the action of specific autolysins, as those experiments demonstrate where the leukemic white blood cells decreased in the same proportion when suspended in the serum or plasma of healthy persons. Consequently the cause of the cell destruction is to be looked for in the lessened resistance of the leukemic cells.

Examination of the ameboid movement of the leukocytes gave negative results.

By the help of Bordet-Gengou's complement-fixation test a specific autolysin was not to be demonstrated.

Animal experiments were valueless in throwing light on the problem.

Conclusion. Based upon these experiments, a specific autolysin incidentally present in the leukemic blood as the primary cause of leukemia is not considered as justified. On the other hand observations are mentioned demonstrating the decidedly lower resistance of the white blood cells in leukemia which leads to their rapid destruction.

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STUDIES ON LEUKEMIA.

II. CONCERNING THE ACTION OF ROENTGEN RAYS.

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SINCE Senn's discovery of the favorable influence of Roentgen rays upon leukemia numerous investigators have been interested in its interpretation. Out of the numerous data gathered in the course of years it may be undoubtedly concluded that the Roentgen rays have an *elective* effect upon the white blood corpuscles as well as upon the leukemic tissues. The method of this action, however, still needs explanation.

In general there were two kinds of interpretation strongly opposed to each other. According to the first the Roentgen rays *directly* injure the white blood cells and the leukemic tissues, and according to the second they act only *indirectly*, that is, under their influence there arises some substance secondarily causing the destruction of the cells. Several call this substance a leukotoxin of lytic effect; others endeavor to define it chemically, looking for it in a decomposition product of the lecithin, in the *cholin*.

The strongest argument of the adherents of the indirect effect is that after use of the Roentgen ray, not only the tissues directly exposed to the rays show alterations of regressive character, but also those affected not at all by the rays. For example, it is a well-known fact that after radiation of the large leukemic spleen not only this organ gets smaller but the liver and the distant lymph glands too.

The experimental work was rendered exceedingly difficult by the fact that we do not possess a reliable method for procuring the white blood corpuscles themselves. Essentially this circumstance furnished the vulnerable point of all the experiments and resulted in the numerous contradictions.

It seemed of interest to reopen the question, therefore, by the method elaborated by me for the isolation of the white blood cells.¹ The experimental technique was the same as published in the previous paper.²

In the first series of experiments I tried to demonstrate the hypothetical Roentgen ray leukotoxin as well as the cholin in the serum or plasma of the radiated patients. Therefore at first I let the serum or plasma of the radiated leukemics react upon the isolated white blood corpuscles of healthy persons of the same sex. On the other hand, to demonstrate the cholin, I systematically examined the patients' blood as well as their urine.

For the determination of the cholin the biologic methods of Reid Hunt^{3*} and of Guggenheim and Löffler⁴ were of great use. Both methods are extraordinarily sensitive, to such an extent that $\frac{1}{10000}$ mg. of cholin may be demonstrated in the form of its acetyl derivate.

Regarding the estimations of cholin I wish to mention that before the exposure I carried out systematic determinations and found that its quantity does not extend to the limits marked by Guggenheim and Löffler as physiologic either in the urine or in the blood of leukemics.

The patients were radiated usually three times over the spleen, the exposures lasting mostly half an hour.

Observations were made on 7 cases, 6 of them being myelogenous and 1 lymphatic leukemia. The experimental results were in every case almost identical, so that I publish only one table (Table I).

Qualitatively the same blood changes were noted after radiation as observed by most investigators: After a short initial leukocytosis the number of the white blood cells gradually decreased, reaching the lowest level three to four weeks after the last exposure. The number of the red corpuscles and the hemoglobin content presented a gradual improvement after the irradiation.

As noted in the previous paper, the white blood corpuscles of healthy persons suspended in leukemic serum showed an average decrease of 20 per cent in twenty-four hours and the ones suspended in leukemic plasma of 23.5 per cent. After irradiation no essential divergence was noted: The cell decrease presented values of 18 to 25 per cent also. Consequently no substance of leukolytic power might have been demonstrated either in the serum or in the plasma of leukemics, four hours as well as two days or even weeks after radiation.

The cholin presented no essential increase after irradiation, either in the urine or in the blood. Even if a greater quantity was found than before, the physiologic limit was never exceeded. Consequently neither the decrease of the white blood cells nor of the hyperplastic tissues may be brought into connection with the cholin.

The supposition would be possible, however, that the hypothetic leukotoxin would present an *autolysin*, reacting with the white blood cells of the individual alone. Therefore it appeared advisable to undertake a series of experiments to test this question. The patient's leukocytes were suspended in his own serum and also in his own plasma. The method was the same as before. At the same time leukemic white blood cells were suspended in the serum or plasma of *perfectly healthy* persons of the same sex.

* By this method cholin has been permanently demonstrated in the urine of healthy persons as well as in their blood. Its quantity varied between 0.002 to 0.1 gm. per cent in the urine and between 0.02 to 0.2 gm. per cent in the serum, expressed in the form of its chlorhydrate derivate.

TABLE I.
(Case XX, Mrs. J. M., aged forty years; myelogenous leukemia.)

Day examined.	Red blood corpuscles, per c.mm.	Hemo- globin, per cent.	White blood cor- puscles, per c.mm.	Per cent.								Cell decrease under 24 hrs., per cent.		Cholin, per cent.		Remarks.	
				Neutrophils.	Eosinophils.	Basophils.	Monocytes.	Lymphocytes.	Metamyelocytes.	Myelocytes.	Myeloblasts.	Nucleated red corpuscles.	In serum.	In plasma.	In urine.		In serum.
April 30	3,000,000	67	780,000	45	3	..	7	11	5	24	5	4	19.3	17.8	0.007	0.050	Before treatment. Four hours after exposure. May 4, repeatedly re-irradiated. May 11, newly irradiated.
31	3,110,000	65	497,000	58	5	..	8	..	7	19	3	6	21.5	17.4	0.013	0.090	
May 1	3,350,000	68	493,000	61	3	1	6	3	8	15	3	2	18.8	20.4	0.019	0.060	
10	3,600,000	70	412,000	64	2	..	5	5	4	19	1	..	20.7	21.1	0.010	0.030	
20	3,570,000	71	302,000	67	3	2	5	7	4	11	1	..	19.3	20.5	0.015	0.080	
30	3,720,000	74	185,000	69	1	2	7	10	2	9	18.4	17.2	0.048	0.160	
June 10	3,960,000	77	84,000	71	3	1	6	14	1	3	1	..	19.1	18.9	0.009	0.088	

Experiments were arranged in 7 cases as before. The results showed a good agreement, consequently I wish to present only one table (Table II).

TABLE II.

Day examined.	Leukocytes, decrease under 24 hours, suspended, per cent.				Remarks.
	Personal cases.		Healthy persons.		
	Serum.	Plasma.	Serum.	Plasma.	
April 30	23.4	28.5	28.3	34.2	Before treatment.
30	54.8	53.7	51.9	56.7	Four hours after the exposure.
May 1	48.2	46.9	44.4	47.1	May 4, repeatedly roentgen rayed.
10	46.5	45.8	40.7	40.1	May 11, newly irradiated.
20	42.3	44.6	40.1	39.2	
30	30.7	31.2	28.6	26.6	
June 10	29.9	22.4	28.6	21.4	

Apparently there was more cell decrease than in the previous experiments arranged with the leukocytes of healthy persons. Especially four hours after radiation the cells diminished very considerably: In 6 of the 7 cases the cell decrease was twice as much as before the treatment. Days after the exposure the destruction became of a milder character, in proportion to the time that passed after the treatment. Radiated again, however, the cell decrease was again higher, clearly illustrating its dependence upon the exposures. One month after the last exposure the cell decrease was about the same as before the treatment.

The cause of the marked cell diminution, however, cannot be looked for in the action of specific *autolysins* arising under the influence of the Roentgen rays, as proved by the experiments when the leukemic white blood cells have been suspended in the serum or plasma of healthy persons. The cell decrease was almost the same as in the patient's own serum or plasma.

Consequently the only supposition that remains is that under the influence of the Roentgen rays the resistance of the leukemic white blood cells is lowered. It, therefore, seems probable that the cell destruction arising in leukemia under Roentgen ray treatment is due to the *direct action* of the rays.

To throw further light on the problem, however, other experiments were undertaken.

At first the *ameboid movement* of the leukocytes, one of their most important life functions, was studied. The observations, however, gave such contradictory results that I would not dare to draw any conclusions from these experiments.

To demonstrate the hypothetic autolysins perhaps present in the serum of radiated leukemics experiments were also undertaken with

the *complement-fixation test*, with the same technique as reported in the previous paper. No positive complement-fixation test was obtained either directly or days or weeks after the exposure, that is, no specific autolysin was demonstrated.

Some investigators have attempted to demonstrate the specific leukolysins by animal experiments, and have found that the animals became leukopenic after the injection of the serum of radiated leukemics. Other investigators, however, did not get this effect. With the idea of undertaking similar experiments, not on animals, but on human beings, and more especially on leukemics, the question was put as to whether the serum of radiated leukemics has any leukolytic power on any *other leukemic patient* previously not treated.

After excluding all possible dangers (syphilis, tuberculosis and so forth) with rigorous asepsis two injections were undertaken. On the first occasion the blood was taken four hours after the irradiation, that is, in the time when the serum could be perhaps considered the most active, and on the second occasion three weeks after the last exposure, when the number of the white blood cells was at its lowest. In both cases 3 cc. of serum were injected intramuscularly.

In both cases the temperature of the patients rose to about 39° C., with chills. Other symptoms did not appear. The blood cell counts showed no mentionable change. After twenty-four hours the patients became free from fever, and the injection caused no unwelcome consequences.

Specific autolysins were thus not demonstrated.

Summary. White blood cells of healthy persons suspended in the serum or plasma of radiated leukemics decreased in number after twenty-four hours' incubation in the same proportion as before the irradiation.

White blood cells of radiated leukemics suspended in their own serum or plasma presented a very marked decrease, especially four hours after the exposure. After irradiation the cell decrease became progressively less with each test and one month after the last exposure it had sunk to the same degree as before the treatment. Nevertheless, the white blood cells of radiated leukemics, suspended in the serum or plasma of *healthy* persons presented also a decrease of the same proportion as when suspended in their own serum or plasma.

The examination of ameboid movement did not give any acceptable results.

No specific autolysin was demonstrated with the complement-fixation test.

The serum of radiated leukemics injected into other leukemic patients of the same sex did not cause any decrease in the number of white blood corpuscles.

The quantity of cholin did not increase either in the blood or in the urine of leukemics under Roentgen ray treatment.

On the basis of these experiments the conclusion seems justified that no specific leukolysin or autolysin will be produced in the leukemic organism under the influence of the Roentgen ray. Consequently the effect of the Roentgen rays in leukemia cannot be explained by this way as well as by the theory based upon the increase of the cholin.

The experiments, however, show that the low resistance of the leukemic white blood corpuscles is very definitely lowered still further by the Roentgen ray treatment. Based upon these experiments the supposition is justified that cell destruction is connected with the *direct* action of the rays.

The effect of the Roentgen ray upon the distant organs or tissues not directly affected could perhaps be explained by the circumstance that under the exposure *electrons* invade the organism and, circulating in the blood, reach all parts of the organism, exerting their deteriorating action upon the sensitive cells and tissues.

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RUPTURE OF THE HEART BY INDIRECT TRAUMA IN A FOUR-YEAR-OLD BOY.

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THE recent interest in rupture of the heart stimulated by Krumbhaar and Crowell's article, leads us to believe it worth while to report the following case: Among 623 cases in the literature dealing with rupture of the heart, Krumbhaar and Crowell find only 4 in the first decade of life. Nuzum and Hagen cite only 1 among their 245 cases, and Chapelle none in a report of 14 cases. Three of the cases of Krumbhaar and Crowell and the 1 of Nuzum and Hagen showed definite myocardial changes, while in Krumbhaar and Crowell's fourth case we could not determine whether or not myocardial changes were observed.*

* We are indebted to Dr. Krumbhaar for giving us full information about these cases.

Report of Case. A boy, aged four years, was struck by a motor truck, which passed over the boy. He was brought to the hospital immediately but died on admission.

Autopsy. Body is that of a well developed, well nourished, male child, aged four years. The body measures 106 cm. in length. there is no rigor mortis but slight livor mortis is present in the dependent parts. Skin and visible mucous membranes are extremely pallid. The skin covering the abdominal wall shows a few recent abrasions covered with a small amount of dried blood clot. The abrasions extend only slightly into the subcutaneous tissue. There is no external evidence of trauma to the chest. On section, the anterior abdominal and chest walls show no hemorrhage or other evidence of injury. Ribs show no fracture.

The peritoneal cavity, especially in the region of the pelvis, contains about 150 cc. of partly clotted, recent blood. Surfaces are smooth and glistening.

The pleural cavities contain no excessive amount of fluid. Surfaces are smooth and glistening.

The pericardial cavity is extremely distended and filled with about 300 cc. of recent bloodclot with some fluid blood. Surfaces are smooth and glistening. There is no evidence of acute inflammatory exudate.

The mediastinal, peritoneal and retroperitoneal lymph nodes are slightly larger than average but show, on cut section, nothing unusual.

The thymus weighs 30 gm. The capsule contains a small amount of clotted blood. On section, a few areas of hemorrhage are noted in the substance of the organ.

The heart weighs 65 gm. The organ shows a rupture extending, in general transversely, from about the midportion of the anterior surface of the left ventricle, across the left margin and ending in the lower third of the posterior surface of the left ventricle, near the interventricular septum. The rupture is 6.5 cm. in length. The wound gapes and the edges are separated about 2 cm. The middle 4-5 cm. of the rupture involve the endocardium, myocardium and epicardium, while 1 cm. at each end involves only endocardium and myocardium, the epicardium remaining intact. The margins of fracture are irregular ragged and covered with clotted blood. The mural endocardium is elsewhere smooth and glistening. There are no antemortem thrombi, nor evidence of acute inflammation. The valve leaflets are delicate and show no pathologic changes. Sinuses of Valsalva show nothing unusual. The mouths of the coronaries are patent, and the vessels show no grossly demonstrable changes. The myocardium of the left ventricle shows on cut section, just below the aortic valve in the anterior wall of the left ventricle, a small oblique rupture 6 mm. in length, involving the myocardium only. The margins



Photographs of anterolateral and lateral aspects of the heart.

here show the same ragged appearance as those of the main rupture. Myocardium otherwise shows no grossly demonstrable lesions.

The aorta is of normal elasticity. The intima throughout is smooth and glistening. There is no evidence of a hypoplasia.

The lungs show no pathologic changes.

The spleen weighs 40 gm. The capsule is smooth. The organ cuts with decreased resistance. On cut section follicles are larger than average and appear to be more numerous. The trabeculae are barely visible. The pulp does not bulge and does not scrape away with the knife.

The liver, kidneys, pancreas and adrenals show no abnormal changes.

Gastrointestinal Tract. The solitary follicles of the lower ileum and ascending portion of the colon are apparently more numerous than average and project above the surface to a greater extent. The Peyer's patches are similarly conspicuous.

Pelvis. The right pubic and iliac bones are the seat of several fractures, with extreme hemorrhage into adjacent fascia, muscle and retropelvic tissue. This is the source of the blood found in the peritoneal cavity.

Histologic Examination. Sections of the myocardium taken from various parts and stained with hematoxylin and eosin show no signs of a degeneration, fibrosis or inflammation. The intercalated disks in areas near the rupture are clearly visible with, in some places, a separation of the muscle fibers along the lines of the disks. In the region of rupture the muscle elements are irregularly broken, independent of the disks. This region also shows a few red blood corpuscles between the muscle fibers. No signs of beginning repair are observed.

Thymus shows a few areas of hemorrhage. No destruction of lymphoid tissue is demonstrable.

Spleen. The follicles are larger than normal and show a few endothelial cells in addition to lymphocytes. No destruction of lymphocytes can be found.

Gastrointestinal Tract. The lymph follicles in the submucosa throughout are enlarged and show chiefly lymphocytes and a few endothelial cells.

Lymph nodes and remainder of the organs show no significant histologic changes.

Summary. A case of rupture of the heart in a boy aged four years, is reported. He was the victim of an automobile accident in which he was struck apparently in the region of the right hip with fractures of the right pubic and iliac bones. There is no evidence of injury to the chest. No pathologic changes other than the rupture in the heart are demonstrable. The lymphoid apparatus in general is hyperplastic. No definite signs of a status thymolym-

phaticus are present. The remainder of the organs show no gross or histologic changes.

We cannot definitely exclude spontaneous rupture. Status thymolympathicus and hypoplasia of the cardiovascular system can be excluded. The myocardium shows no evidence of previous disease. While blows to the chest cannot be excluded, we saw no evidence of injury to the chest wall. Therefore the most probable explanation is that the rupture of the heart is dependent on the trauma of which the greatest force was exerted in the region of the right pelvis.

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THE NATURE AND DISTRIBUTION OF THE LESIONS IN SYPHILITIC AORTITIS.¹

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In a series of 300 postmortems, 33 cases have been observed that show gross or microscopic lesions that correspond with the generally accepted description of syphilitic aortitis. There were a few cases with very slight microscopic changes, some evidently due to syphilis, that were not included in this series. Most of these had more or less sclerosis and no very marked gross changes that could be attributed to syphilis.

In the 33 cases, 29 had marked gross lesions in the first part of the aorta and 16 had marked aneurysms. There were 14 cases in which the aneurysm involved the ascending aorta and arch, 2 where it involved the descending aorta and 2 cases that had an aneurysm of the ascending aorta and 1 of the descending. In 3 cases, there was marked calcification. In 5 cases, the lesions were mild. One of these was ten years of age and the diagnosis could only be made from microscopic sections. There were 19 cases with various valve lesions, 13 of these showed changes in the aortic valve that were evidently syphilitic.

Our postmortem material is obtained from private cases, through the members and friends of the El Paso Clinical and Pathological Club, and from the coroners; hence it represents a fair average of all sorts of people.

¹ Read before the Texas State Pathological Society at Austin, May 4, 1925.

From a study of this material it can be stated that the disease may be either localized or general and may be mild or severe. That portion of the aorta inside the pericardium or the ascending aorta usually suffers most severely but the remaining portion may also suffer in like manner. Marked gross lesions, like aneurysms and extensive scarring, are due to a severe but gradually progressing process like a serpiginous ulcer which destroys the media. Where the disease is mild and slow, no marked scarring or distortion results though the media may be found made up completely of scar tissue and it is often impossible to diagnose the condition without sections. The condition is chronic and progressive and unless interrupted by treatment, will eventually destroy a portion of the aorta.

The fundamental lesion, generally accepted, in syphilitic aortitis is a periarteritis and obliterating endarteritis of the vasa vasorum. In carefully examined cases considerable variation will be found. In the periarteritis there is a mild to a marked accumulation of round cells around the vessels and in many places small vessels are being obliterated. Occasionally, giant cells, not unlike those of tuberculosis, may be present. These various cell accumulations may form miliary gummata. Either coincident with these changes or soon after, there appears considerable increase of fibrous tissue in the adventitia and there is also more or less destruction of the media and, at times, a vegetative deposit may appear on the intima.

The extent of injury to the aorta depends on the extent and rapidity of the process in the adventitia though most damage is done to the elastic layer and it is the injury to this coat that causes serious clinical conditions.

The ultimate anatomic result of a syphilitic aortitis seems to be dependent upon the origin and distribution of the vasa vasorum. No record was found as to their origin but it seems from a general examination that for the ascending portion they originate in the coronaries. Those supplying the arch come from the first intercostals and bronchial and the descending is supplied by the intercostals. Therefore, in the first portion, there is a relatively long and large area supplied by a set of long slender vessels while in the remainder, the area supplied is relatively small and the vessels short.

The elastic layer is supplied with blood by branches of the vasa vasorum and any serious occlusion of any one of these vessels would cause a corresponding area to suffer in the elastic layer. When the periarteritis and obliterating endarteritis are severe enough to stop the circulation in any individual vessel, that is just what happens. The area of elastic layer supplied by the occluded vessel starves and dies, becoming infarcted. As soon as this occurs, an effort is made to repair the injury and, on the intimal wall, a heavy layer of fibrin is deposited to cover the injured area. At the same time the elastic layer breaks up and round cells rush in to carry away the debris. The gross picture produced is that of an



FIG. 1.—Heart is from Case I, reported in the paper. Anterior wall of the left ventricle cut away to expose the root of the aorta. The pins are inserted just above the openings of the coronary arteries. The right is closed with fibrous tissue and the left is surrounded by necrosed and coagulated exudate. The tissue of section A was removed from near the right coronary and the greatly thickened wall of the aorta is apparent in the turned-out edges.

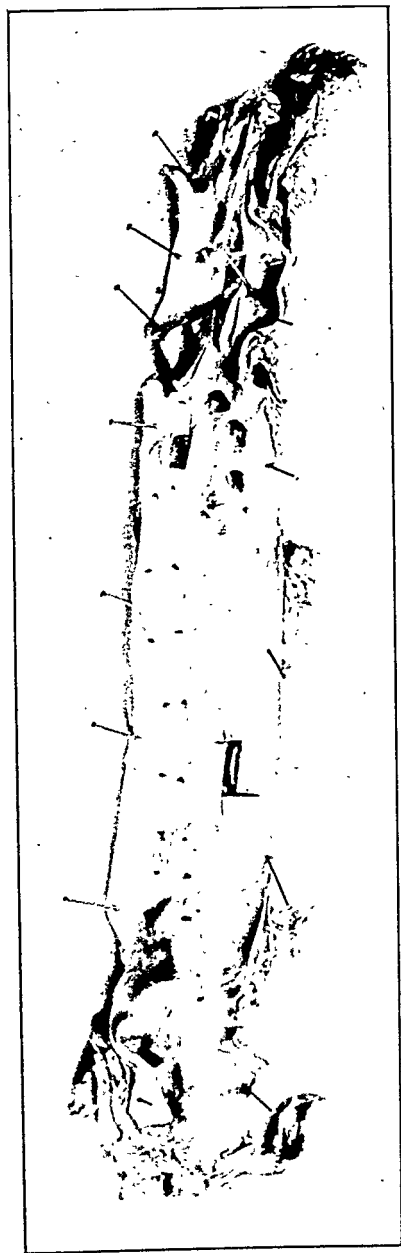


FIG. 2.—The aorta from the same case as Fig. 1. This shows all of the intercostal openings perfect with no marked gross lesions anywhere present. Section *E* was made from the area removed in the thoracic portion.



FIG. 3.—This shows an aneurysm in the thoracic aorta and in the region occupied by the aneurysm, the intercostals are obliterated.

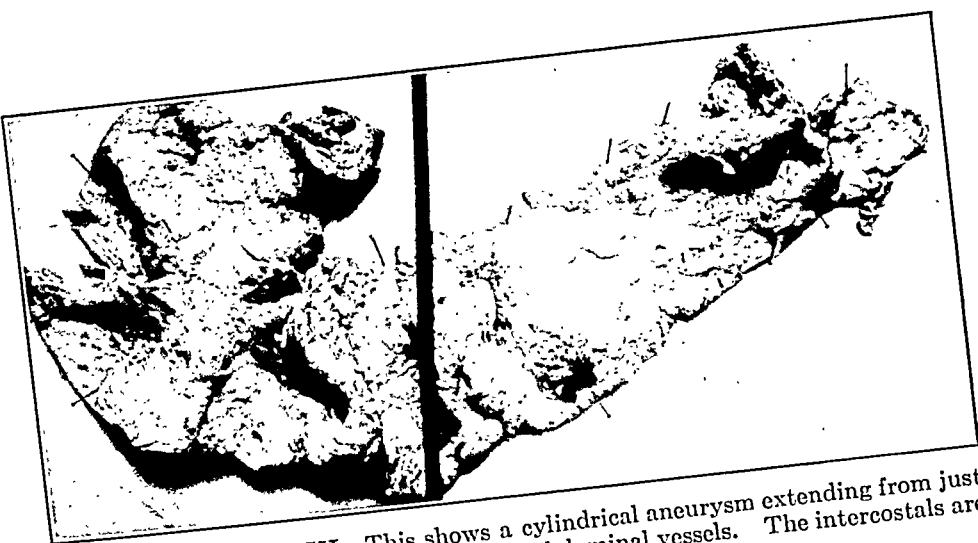


FIG. 4.—From Case III. This shows a cylindrical aneurysm extending from just above the aortic valves down to the great abdominal vessels. The intercostals are practically all obliterated in the portion occupied by the aneurysm.



FIG. 5



FIG. 6

FIGS. 5 and 6.—Photomicrographs of section A from Case I. Fig. 5 is stained with hematoxylin and eosin and Fig. 6 is stained with orcein. In Fig. 5 the large infiltrated area of round cells is visible as a darker grayish deposit. In Fig. 6 the elastic fibers are shown broken up.

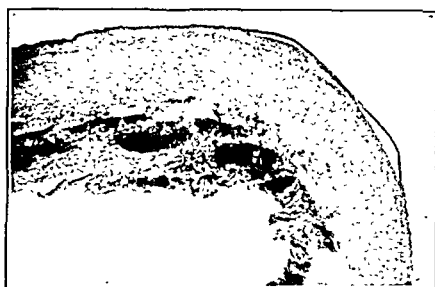


FIG. 7.—Photomicrograph of section *C* from Case I. The round cell deposits are present as dark oval masses. The elastic fibers showed a very slight change in this area.

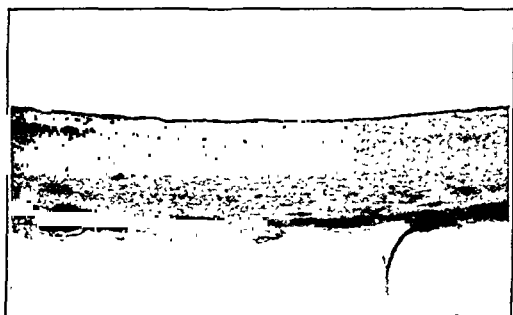


FIG. 8

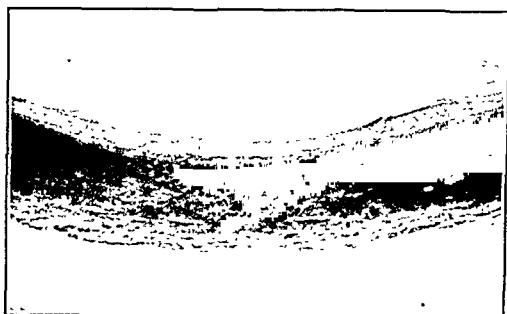


FIG. 9

FIGS. 8 and 9.—Photomicrographs of section *E* from Case I. Fig. 8 is stained with hematoxylin and eosin, Fig. 9 is stained with orcein. Fig. 8 shows a black deposit of round cells in the adventitia and some small islands in the media. Fig. 9 shows a slight thinning out of the elastic fibers.

ulcer and if the disease progresses, we have a creeping ulcer. If the area of elastic layer destroyed is very large and destroyed rapidly, the adventitia is unable to maintain the pressure without stretching and an aneurysm is started. If the ulceration spreads fairly rapidly, the aneurysm grows larger. There is no elastic layer in the aneurysmal wall because it was destroyed before the sac was formed and it is not replaced once it is destroyed. It is evident that an aneurysm will form easier in or near the arch than at the ring where the outside supports are more extensive. The extent and severity of the process also have some relation upon the form of the aneurysm produced. Where there is a relatively small, severe and rapid ulceration, the elastic layer is rapidly destroyed over a small area. The corresponding portion of the adventitia gives way over this and we have a sac with a definite neck and a relatively small opening. Where the process is a little slower and more extensive, a larger area of adventitia stretches and no definite neck is produced. Or if the process continues, we have an aneurysm made up of several pouches, each pouch representing a new area of reaction. In those cases where aneurysm occurred in the descending aorta, the intercostals supplying the portion occupied by the aneurysm had been obliterated and the wall of the aorta showed extensive scarring.

One case serves to illustrate the early part of the process well. This occurred in a robust Mexican man who fell over dead on the street. No history was obtainable except that he had worked up until recently and was about twenty-five years of age.

Postmortem examination revealed the following important lesions. The heart was about normal in size and the right side was healthy. In the left side there were recent infarcts in the tips of both papillary muscles. The mitral valve was healthy. At the base of the aorta there was a lichen-like process that included the aortic valves and a strip, 25 mm. wide, above. The process began in the right half of the posterior valve and sinus of Valsalva and advanced toward the right valve. This was included in the process and, coincidentally, occluded the opening of the right coronary which was closed with fibrous tissue. The leaflet of this valve was considerably thickened, rolled in and contracted. After completely involving the right valve, the process continued and involved the right half of the left valve. Above the junction of the right and left cusps, a small aneurysm was present. That portion of the process involving the posterior and right valves appeared somewhat healed as compared to that involving the left valve. This latter area showed signs of marked activity, the intima was greatly thickened, grayish and red in color, and suggested a vegetative deposit on the wall of the aorta. This condition surrounded and almost occluded the opening of the left coronary. This material was rather friable, easily scraped off and the infarcts in the papillary muscles were proof that some of it had gotten into the circula-

tion. The left coronary was free though the opening was nearly occluded with the fresh vegetative deposit mentioned. The opening of the right coronary was closed with scar tissue. Beyond this, for some distance, the lumen was free and near the intraventricular septum there was a recent reddish antemortem clot, 33 mm. long. The portion between the mouth and thrombus was filled with unclotted blood. There was no recent infarct in the muscle supplied by this vessel. There were however several definite white nodules, 3 to 4 mm. in diameter, in the muscle supplied by this vessel. It would seem therefore that when the opening of the right coronary was closed by the inflammatory process, some particles were dislodged and caused infarct in the heart muscle supplied by it. If this supposition is correct, the process must have been active around the opening of the right coronary for some considerable time previously or, in other words, the process advanced quite slowly. The remainder of the aorta showed no extensive gross lesions and was quite elastic. There was a small sclerotic scar in the arch, such as is frequently seen. In the thoracic portion there were small raised nodules in the intima and at the bifurcation, there was a definite, raised white nodule.

Sections taken from several portions of the aorta were as follows: *A*, the advancing margin of the ulcer including a portion of the aorta that grossly appeared uninvolved; *B*, an older part of the process near the aneurysm; *C*, the ascending aorta above the ulcer where the wall seemed in good condition; *D*, the arch at the scar; *E*, the thoracic aorta; *F*, the abdominal aorta, opposite to the opening of the celiac axis; *G*, at the bifurcation through the thickened nodule there.

Section *A* shows, in a general way, a portion of the aorta before ulceration has commenced and a portion where ulceration is in progress. In the intima at the very margin of the ulcer, the first signs of the advancing disease is a gradually increasing layer of round cell infiltration being at first only one or two cell layers thick and gradually increasing to several layers lying against the media. The media in this region is for the most part quite normal in appearance. In the deeper layers however, small streaks of round cell infiltration begin to appear which gradually widen out toward the disease process. In the adventitia just beneath the media there is a dense, round mass of round cell accumulation which appears surrounding small vessels. The lumen of some of these vessels is largely obliterated with a delicate endothelial growth. Other vessels that are only partially surrounded also show some overgrowth of the endothelium. Further out in the adventitia there are strands of rather dense connective tissue bands interspersed with bands that are much looser in appearance. The process thus far described has been the most advanced part of the

process. As we move back a little where the action is more severe, the round cell distribution in the adventitia becomes as a rule more diffuse, though there are large circular islands of round cells still remaining and more small vessels that seem to be partially or completely obliterated. In the media, in about the central portion, there is still more increase of round cells and the specimen stained with orcein shows the elastic fibers beginning to break up. Further into the lesion the elastic fibers show much more destruction with increased round cell infiltration and under the intima, there is a large deposit of necrotic material almost free of cells. In places, this looks like a coagulative necrosis. Still further into the process, round cells commence to appear in this necrotic material; the media gets thinner and thinner and finally a point is reached where the round cells extend from the intima in a great mass into the adventitia, the elastic layer being completely broken up and the orcein stained specimen shows very few of the fibers remaining. Where this intense cell accumulation is, many of the cells are polymorphonuclears, especially under the intima; in the adventitia they are practically all mononuclears. In the adventitia, the round cell infiltration has become more diffuse, there are more vessels showing obliteration but islands of round cells also remain. On the outside of the adventitia, there is a considerable layer of fatty tissue with much round cell infiltration in it. The fat is in rather small areas and is somewhat cut up by radiating bands of fibrous tissue.

Section *B* shows the area of fat in the adventitia somewhat increased in thickness and also cut up by radiating bands of fibrous tissue and still contains islands of round cells, particularly under the very outer margin of the adventitia. Partially and completely obliterated vessels are still present. The fibrous and muscular layers of the adventitia seem to be more dense than formerly. In the media in places, the orcein stain shows the elastic fibers replaced with a dense layer of paler staining fibers like fibrous tissue. These fibers are much finer than the original elastic fibers, the layers are of varying degrees of thickness and the fibers are much interwoven. In places, remnants of the elastic fibers still remain. Beneath the intima, there is a large amount of necrotic material containing very few cells. In the media, where the elastic fibers have been destroyed, there is still round cell infiltration and a considerable growth of new vessels. One very striking thing is that the delicate elastic fibers scattered in the adventitia seem to be preserved without injury.

Sections *C*, *D*, *E* and *F* all show round cell accumulations and obliterating vessels in the adventitia, being most marked in section *C* and least in *F*. The round cell infiltration in the adventitia, next to the media, is everywhere marked. The media shows changes in all the sections, round cell infiltration and the orcein stain shows the fibers staining poorly and gradually being replaced by fine fibrous

tissue. Section *F* shows a laminated, structureless deposit on the intima which accounted for the thickening and changes in the adventitia like those in the other sections.

The case just reviewed shows the early changes. Two other cases illustrate the later changes very well.

One, a man aged 47, died suddenly of a large hemorrhage from the mouth. Seven years before, he had a pain in the chest. Roentgen ray showed a definite enlargement of the ascending aorta and his condition was diagnosed as an aneurysm. He was given anti-syphilitic treatment and improved, the aneurysm getting smaller and the aorta appeared normal by Roentgen ray examination.

Postmortem examination showed the whole aorta uniformly dilated and scarred. The aortic valves were not involved. There were numerous thin calcified deposits in the intima showing the condition to be rather old. The whole wall was rather thin. Just past the crest of the arch was a recent aneurysm on the anterior wall which lay against the esophagus. This had ulcerated at the point of contact and had ruptured into the esophagus. The aneurysm was not very large and the aortic surface was covered by an organized clot. This latter condition was the result of some recent activity.

A second case of an old Mexican, who died of pneumonia, showed the whole aorta dilated, the ascending more than the rest. There were no distinct pouches. All of the intercostals and bronchial were completely obliterated. Even the left carotid was very small, the opening being almost closed up. There was considerable calcification throughout the intima. The most striking condition present was the greatly thickened condition and vascularity of the adventitia. Evidently the circulation feeding the coats of the aorta was reestablished in the adventitia. The whole change must have been rather gradual and also diffuse.

Most of the other cases furnish evidence to sustain the explanations given above but further proof seems unnecessary.

Summary: in a series of 300 postmortems, 33 cases of syphilitic aortitis were observed. From a study of these cases it can be stated that syphilis may attack the aorta either locally or generally, more usually the latter. One portion may suffer severely and the rest only slightly. The first or ascending portion usually suffers most and the rest less severely; but the whole process is similar and is a strangulation necrosis caused by periarteritis and obliterating endarteritis of the vasa vasorum which starves and destroys the elastic layer. When the condition is violent, it travels as a serpiginous ulcer, causes aneurysms and a vegetative growth on the intima which may break off and form emboli. The most usual site for serpiginous ulcers is in the first portion, apparently due to the anatomical structure; but the ulcers, wherever found, are due to a sudden cutting off of the blood supply to the area involved.

TENDER SPOTS ON THE CHEST WALL IN ANGINA PECTORIS.

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FAR from having an equivocal implication, tender spots on the chest wall in angina pectoris are a most important and significant sign. Most clinicians, who have given careful study to angina pectoris, interested themselves deeply in this question; not alone because it is related closely to the question of pain in cardiac affections, but because, as a physical sign, it is an interesting observation of reflex referred pain.

Aortic and coronary lesions in angina pectoris lead to secondary changes in the heart wall by interfering with its nutrition. The left ventricle and aorta are, on account of the higher pressure to which they are continuously subjected, much more liable to degenerative changes than the right ventricle and pulmonary artery, producing direct irritation of their nerve endings. In all lesions belonging to this group, cardiac pain is of frequent occurrence.¹ Some pain and tenderness may exist over the precordial region in acute pericarditis, but anything approaching the typical symptoms of fully-developed angina pectoris is undoubtedly rare.

Peter made clinical observations of tender spots localized in the precordium and preaortic regions.² He assumed that the points of tenderness were approximately located directly over the affected area in the heart wall. He found the points mainly over the fourth and fifth intercostal spaces in the region of the heart apex. Other sensitive spots were localized in certain cases in the third space to the left of the sternum, and sometimes also in the axilla and posteriorly. In cases with aortitis, Peter found tenderness over the second intercostal space to the right of the sternum.

In recent years, the condition of the susceptibility of the skin, tested objectively, has yielded most interesting results. The observations of Mackenzie and Head have led to a new era in the investigation of the affection.³ As Head has so well put it, "The sensory localizing power of the surface of the body is enormously in excess of that of the viscera, and thus by what might be called a psychological error of judgment, the diffusion area is accepted by consciousness, and the pain is referred on to the surface of the body instead of on to the organ actually affected."⁴

Over considerable areas of the surface of the body, corresponding, with more or less accuracy, to the regions in which pain is subjectively felt, there is an exaggeration of sensibility. This hyperesthesia in angina pectoris is most commonly experienced over the upper

intercostal regions and the sternum, but it may be ascertained to be present over part of the neck and arm as well. Tenderness may be discovered by the application of varying degrees of pressure with a blunt or with a sharp instrument, or by gently pinching the skin with the finger and thumb. In some instances, after pain and tenderness have been present for a considerable time, the latter is succeeded by anesthesia.

Head's explanation of hyperesthesia in association with pain has received general acceptance. Impulses passing to the cord from a diseased viscus produce a disturbance in the segment to which they



FIG. 1.—Case F. L. Four months after onset of severe angina pectoris.

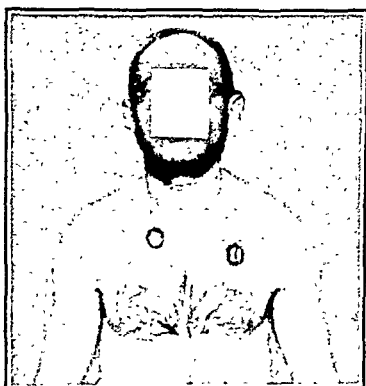


FIG. 2.—Case M. F. Three weeks after first severe attack.

pass; so that any stimulus applied to the area connected by sensory nerves with the segment will be more powerful in its effects and will give rise to exaggerated sensations. When the stimuli are too intense or long continued, the hyperesthesia may give place to anesthesia.

Head, Fränkel, Allbutt and others sought evidence of cutaneous hyperesthesia in angina pectoris. These they found on the upper part of the chest, front and back, toward the left side and the left arm for a short time after the attack. They also found tenderness of the muscles of the area affected. Allbutt states that these were inconstant and the sensation of hyperesthesia fleeting.⁵ But they

were not fully verified by physical examination. It thus appears that Allbutt's assertion of the inconstancy of this symptom of local tactile tenderness and sensitivity on the chest was based upon statements made by the patients and not upon objective physical study. Frequently the tenderness over the front of the chest is such that the patient constantly shifts his shirt from it or wears his vest unbuttoned.

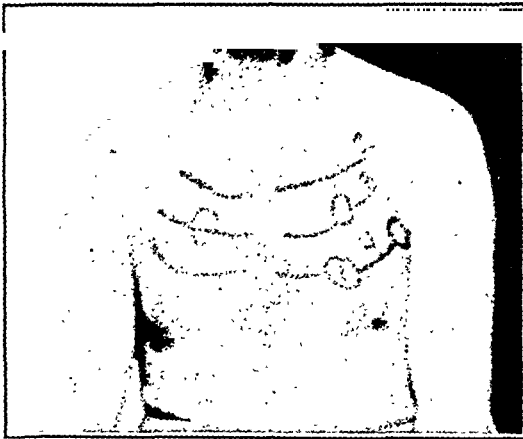


FIG. 3.—Case B. S. Ten days after first severe attack of angina pectoris.

In eliciting this sign, we have endeavored to use uniform pressure by means of the thumb or the tip of the finger over the sternum and the ribs on each side. The periosteum of the ribs seems to show greater sensitiveness to pressure than the skin and seems to respond through the corresponding spinal segment to a much lower stimulus; that is, very slight pressure over the rib will elicit hyperesthesia or tenderness where greater stimulus would be required to induce a response from the skin or the intercostal muscles. Suddenly, the patient will assert a degree of tenderness over a certain point. This can be recorded, as I have done in my cases, by a circle painted with tincture of iodine. Several spots may thus be elicited and the chest then photographed for future reference (Fig. 1).

In a study of 55 patients with angina pectoris in whom this sign (tender points on the chest wall) was carefully looked for, it was absent only in 7 cases. In 13 other cases and a larger number of cases of mitral stenosis not classified here, tender points were discovered by intensive pressure over the ribs. The diagnoses in these cases were as follows: Aortitis, 2 cases; aortic roughening, regurgitation and arteriosclerosis, 1 case; rheumatic mitral stenosis and regurgitation, 3 cases; rheumatic myocarditis, 2 cases; diabetes with lues, 1 case; hypertension with aortic sclerosis, 2 cases; paroxysmal dyspnea with chronic myocarditis, 1 case. In the routine examinations of a large number of normal individuals, tender spots on the chest wall were not found in any case. We are, of course, leaving out of consideration cases of multiple myeloma or other affections in which the ribs may show tenderness.

At first I have attempted to classify the cases as to whether they were predominantly of aortic or of coronary involvement. It is evident that such a classification cannot be made with precision since it is well known that in angina pectoris, coronary involvement is a condition usually concomitant with the aortic lesion (see table).

LOCATION OF TENDER SPOTS ON CHEST WALL.

Location of tender spots.	Number of cases to left of midline.	Number of cases to right of midline.
First rib and clavicle	0	2
Second rib	7	3
Third rib	18	13
Fourth rib	14	1
Fifth rib	7	1
Sixth rib	2	1
Seventh rib	1	1
Total	49	21
Sternum		5
Epigastric		2
Posteriorly		4

However, it is noted that the tender points are present in the largest number of angina pectoris cases (39) in the upper left pectoral region (fourth cervical—second and third thoracic). In 9 cases, there were tender spots localized over the aortic area on the right side and the outer part of the right pectoral region (fourth cervical). Tender spots were also present in 8 cases over the gladiolus and the right parasternal region (third, fourth, fifth and sixth thoracic). Tenderness in the epigastrium was present in 2 cases (sixth and seventh thoracic). In a large number of cases, tenderness was also present in the left axilla (second to fourth thoracic and often third and fourth cervical). This was encountered especially shortly after an attack of anginal pain. The tender spots in the left axilla are to be referred to the large lateral branch (the intercostohumeral)

of the second thoracic which extends outward and backward to the arm. In a few cases they were also present posteriorly on either side of the spine, more often to the left of the fourth, fifth or sixth dorsal vertebra.

A very large number of cases of angina pectoris present tender points localized in the outer part of the right pectoral region, over the second and third ribs. These are obviously associated with the lesion affecting the aorta. Schmoll⁶ and Gibson assumed that angina pectoris with radiation to the right side implied involvement of the right side of the heart.

The distressing or painful symptoms that accompany an attack of angina pectoris usually subside with the immediate improvement of the patient. The tender spots, however, on the chest wall persist for a very long time and sometimes continue throughout the intervals between attacks. They were, of course, most marked soon after an attack. They persisted, however, in most of the cases throughout the intervals. Where we had the opportunity to reexamine patients from time to time, we found the tender spots fairly constant in their localization. When several areas were sensitive, they sometimes varied in degree of tenderness.

These tender areas on the chest wall have not only a physiologic interest, but a very practical clinical value. In the differential diagnosis between myocardial lesions and lesions affecting other structures, such as the upper abdominal viscera, the finding of these tender areas on the chest wall, particularly on the ribs, is an important observation.

Conclusions. Hyperesthesia of areas on the chest wall is commonly found in association with anginal pain. It is referable to the impaired nutrition of the heart wall and the sensitiveness of the aorta and coronary artery area. It is often complained of by the patient and can be definitely localized objectively.

Of 55 patients with angina pectoris, 48 presented tender spots along the ribs or on pressure over the sternum. This sign was found positive in nonanginal cases with aortic or myocardial disease. In individuals without heart involvement, tender spots on the chest wall were not found in any case.

In cases of angina pectoris, the tender spots are most often located on the second, third and fourth ribs to the left of the sternum (fourth cervical and second and third thoracic) and over the second and third ribs in the outer part of the right pectoral region (fourth cervical).

The tender spots on the chest wall persist for a long time after an attack of angina pectoris and sometimes continue throughout the intervals between attacks.

They are especially valuable in the differential diagnosis between myocardial lesions and affections of the upper abdominal viscera.

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CHRONIC CHOLECYSTITIS.AN ANALYSIS OF 100 CONSECUTIVE CASES DIAGNOSED WITH
CHOLECYSTOGRAPHY AND TREATED BY CHOLECYSTECTOMY,
IN WHICH THE END RESULTS WERE INVESTIGATED.

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IN the two and a half years succeeding the publication of the first paper on cholecystography by Graham and Cole,¹ numerous reports have been published about the procedure, most of them being personal experiences with its use as a diagnostic measure.

Although this method is intended primarily as a diagnostic aid, we must not lose sight of the fact that it is also most valuable as a means of studying the normal physiology of the gall bladder. Use has been made of it for this purpose by many, notably Whitaker and his associates,² and Copher and Kodama.³ By combining their experimental with the clinical diagnostic results we are able to appreciate its true value as an index of the pathologic physiology of the organ.

Cholecystography is a test of the latter, rather than of the structural changes in the gall bladder wrought by an inflammatory process. Such changes, which are easily made out upon gross inspection of the organ, are the end results of the inflammation. When they occur the function of the gall bladder may have long been destroyed, the clinical history and symptoms of the patient readily determine the site of the disease and then the cholecystogram is corroborative evidence and not the important factor in the diagnosis that we know it can be earlier in the course of the disease. It is like relying upon the Roentgen ray in the diagnosis of pulmonary tuberculosis when the patient already has the physical signs of extensive cavitation and is raising sputum laden with tubercle bacilli.

The cholecystogram is of prime importance in the diagnosis of

cholecystitis in the early stages of the disease, at the time when the organ is not functioning properly, when the organic inflammatory changes are not yet marked and at a time when even the gall bladder, *in situ*, may appear to be very little changed from the normal.

In the course of the writer's work in the surgical laboratory of this clinic, he has had the privilege of examining the surgical specimens routinely submitted from the Barnes Hospital. During this time cholecystography has been introduced, and since its advent he has noted a gradual change in the gall bladder material removed at operation, and with it has come a clearer understanding, by the surgeon, of what constitutes cholecystic disease.

Prior to 1924 before a surgeon would operate to remove a gall bladder he would satisfy himself as to certain facts in the patient's clinical history and certain symptoms. These would be the age of the patient, chronic indigestion, pain under the right costal margin radiating around to the back and to the right shoulder, the periodic recurrence of these attacks, associated with nausea and vomiting, constant eructation after meals, the presence of jaundice and of clay-colored stools. One or more of these might be absent, but any of them, associated with tenderness in the gall bladder region, was adequate evidence of disease of this organ and justified operation. These are referred to hereafter as definite symptoms. Such findings usually resulted in the removal of a gall bladder, definitely thickened, quite often reduced to a mass of scar tissue, containing stones in many cases, and adherent to the surrounding structures.

In another large group of cases there would be the complaint of "dyspepsia," and symptoms very much like those of gastric or of duodenal ulcer. In spite of negative laboratory tests for the two latter conditions, exploratory laparotomy was frequently done, only to find a gall bladder slightly to moderately thickened, and sometimes with adhesions on the surface. A third type of case was where an appendectomy, or some other abdominal operation, was being carried out and, upon exploration, a grossly diseased gall bladder was found, which might or might not have given noticeable symptoms.

As confidence in the reliability of the cholecystogram has grown, the above criteria as indications for operation have been to some measure supplanted by the Roentgen ray findings after the administration of sodium tetraiodophenolphthalein. With the establishment of the test as part of the routine gastrointestinal Roentgen ray series in this clinic, several facts have been brought out: (1) It seems to serve as infallible corroborative evidence in those cases where the usual definite symptoms referable to gall bladder disease have been present. (2) By the absence of a shadow it reveals involvement of the gall bladder in those fewer cases which have escaped the usual definite symptoms (about 30 per cent in our

series). (3) In a large group of cases, when the tetraiodophenolphthalein is given intravenously there may be no shadow at all, or a faint shadow which is gone at twenty-four hours; stones or other definite lesions, such as pericholecystitis, may be revealed.

In the normal series of cholecystograms, when the dye is administered intravenously, the shadow is present at four hours, and at eight hours there is noted a change in the size of the gall bladder image, with variation in intensity at some time during the examination.⁴ This ability of the gall bladder to concentrate the dye is an important point in the diagnosis.

In the cases of the third group mentioned above, the gall bladder failed to give a shadow, or when an image was obtained it was faint, due to the inability of the organ to concentrate the dye. Upon exploration, the majority of these gall bladders proved to be but slightly thickened, and with or without some external adhesions. At the same time these were patients in whom the symptoms were of an indefinite nature, that is, "dyspepsia," eructation, vague abdominal pain or distress. With such an indefinite clinical history and, at operation, no other abdominal lesion to account for the symptoms, with only the definite cholecystographic evidence upon which to rely, the question arises in the minds of many, to what extent can one depend upon cholecystography?

In order to determine this, a review and analysis was undertaken of 100 consecutive cases of chronic cholecystitis treated with cholecystectomy, in which the cholecystogram was used in the diagnosis. After reexamining the gross specimens and the slides they were divided into four groups, as follows:

Group.	No. of cases.	Gall stones.	Condition of gall bladder.
A	33	Present	Thick, scarred.
B	8	Absent	Same as Group A.
C	7	Present	Thin-walled, translucent to slightly thickened.
D	52	Absent	Same as Group C.

GROUP A. Grossly these 33 gall bladders were thick and fibrous, some reduced to a mass of scar tissue. All contained stones. Microscopically, there is marked round cell infiltration throughout the whole, thick wall. The mucosal epithelium may be intact or may be missing in places. Buried in the scarred wall are small, gland-like areas of mucosal epithelium, separated from the lining mucosa by the sclerosing inflammatory process. When a small piece of liver was removed for examination it invariably showed lymphocytic infiltration of the periportal areas. Twenty-two of these 33 patients gave the definite clinical history and symptoms usually attributed to cholecyctic disease. The remaining 11 gave the indefinite symptoms already referred to. This group, then, is made up of those cases which we have seen commonly from the day Langenbuch removed the first gall bladder in 1882. Most of these cases (66 per cent) gave a definite clinical picture of cholecyctic disease.

GROUP B. Five of these 8 cases gave a definite history and the other 3 did not. This group differs from the preceding one only in the fact that no stones were found in the gall bladder.

GROUP C. This is made up of 7 cases, 4 of which gave definite symptoms and the remaining 3 did not. Grossly, the gall bladders removed from these patients were but slightly thickened and the mucosæ intact. They contained gall stones, which were not suspected in 5 of the cases until the gall bladders were opened. This was because the latter were distended with bile and the few small stones could not be palpated in this fluid medium. None of these stones gave any shadow with the cholecystogram.

GROUP D. In this group were placed 52 patients. Only 18 of them gave symptoms or histories which definitely pointed to cholecystic disease. The remaining 34, or 65 per cent, gave histories or symptoms to which we have been alluding as indefinite, that is, dyspepsia, eructation, epigastric pain, relieved by soda and duplicating gastric or duodenal ulcer, vague, diffuse abdominal discomfort and so on. Such a history, plus cholecystographic evidence of abnormality, has been our justification for operation. In some of these cases the cholecystogram has shown no shadow at all, while in many there has been a shadow which has been very faint, or absent at four hours, hence, delayed appearance, and has been much fainter than the normal image at eight hours, which is the time of maximum density in the normal gall bladder (if a series of four, eight and twenty-four hour films are taken), and at twenty-four hours the shadow is gone or very faint. Such a cholecystographic series demonstrates the impaired ability of such a gall bladder to concentrate its contents and so indicates that this gall bladder is physiologically pathologic.

Upon laparotomy, in these 52 cases, the gall bladders *in situ* were found to be thin, distended and characteristically bluish in color. Many were slightly to moderately thickened, while others showed no appreciable thickening. Often on the surface were a few delicate adhesions, binding the organ sometimes to the duodenum, or omentum, or pylorus, or more densely to the liver. After removal these gall bladders were found to have thin or slightly thickened walls and intact mucosæ. In 10 of these 52 one saw on the mucosa the characteristic honeycomb, yellow deposits of cholesterin. Microscopically, the mucosa in every case was intact. Deep beneath it, in the muscle layer and extending to the serosal surface, or to the area adjacent to the liver, there was, in all but 8 cases, diffuse lymphocytic infiltration, in no case extensive, but usually slight to moderate. In the small piece of liver, routinely excised, there was always found infiltration of the periportal spaces with lymphocytes, varying from very slight to moderate in degree.

Discussion. The 41 cases making up Groups A and B are the types which we have always seen, where the gross and microscopic findings represent the end stage of a chronic inflammatory process.

Symptoms are always present and in nearly 70 per cent of the 41 cases they are characteristic of gall bladder disease. As mentioned above, the cholecystogram is here a laboratory check and corroborates information already gained by a careful history and physical examination. In the remaining cases, slightly over 30 per cent of these 41 cases, where symptoms are present, but not characteristic, the cholecystogram definitely localizes the site of the disease. In the literature upon cholecystography, which consists mostly of personal experiences with the procedure as a diagnostic test, the reports which are most laudatory are those dealing with cases of this type. To the writer, however, it is in the 52 cases of Group D and the 7 of Group C, and cases similar to them, that the cholecystogram has proven itself of inestimable importance. It is in the interpretation of these cases that too little has been said. To repeat a statement several times mentioned, the cholecystogram is an index of physiologic function, and this fact alone makes it the prime diagnostic feature in cases of the type included in this group of 59 cases.

In the days before cholecystography the writer has seen many such patients explored, the gall bladder inspected, quite often inadequately, as through a low right rectus incision, sometimes palpated without being seen satisfactorily, pronounced normal on the basis of such an inspection, left in place, and the patient continued to have the same symptoms. Many of such gall bladders were probably diseased, with the process at an early stage, when physiologic function was already destroyed or impaired, but with no visible gross change, which is an end stage in the disease, yet apparent.

Intelligent and proper interpretation of cholecystographic plates have changed all this. When the shadow is absent or retarded in appearance and not so dense as in the normal, although the gall bladders may grossly show little or no change, such gall bladders are not functioning normally and should be considered as being pathologic. This has been the view adopted by Graham and his associates,⁵ and arrived at independently by the writer from a study of the histories and specimens of these 100 patients. In 8 of the 52 in this last group there was no appreciable change microscopically in the tissue, at least not enough to account for the patient's symptoms. In the remaining 44 the changes were at no time as marked as in those cases in Groups A and B. In every case of these 52 when a small piece from the edge of the liver was also removed there was round-cell infiltration of the periportal spaces, no matter what the degree of change in the gall bladder might be. This is merely a reiteration of the fact which was brought out by Graham⁶ and later corroborated by him and Peterman,⁷ experimentally. This is a striking feature of those 8 cases in which there was no change microscopically in the gall bladder wall. Whitaker and Fried⁸ have shown that extensive destruction of the liver with chloroform results in nonvisualization of the gall bladder in otherwise

normal animals, but with moderate liver destruction a shadow may be obtained. Chloroform causes destruction of the central portion of the liver lobule, while in our material the inflammatory reaction was always periportal and was also insignificant when compared with the usual chloroform necrosis. In the experiments noted above the absence of a shadow depends upon the fact that so much liver is destroyed that its secretory function, for the time, is so impaired that not enough of the dye reaches the gall bladder to give a shadow. In our surgical material the absence of the shadow cannot depend on any such mild change in the liver, but on a condition seated in the gall bladder, an inability to concentrate its contents.

We may ask ourselves, "Are we justified, from the facts as stated, in regarding these as pathologic gall bladders?" The answer is in the affirmative for the following four reasons:

1. The history of the patient, especially if a definite one. When indefinite there is invariably the complaint of "dyspepsia." This symptom of cholecystitis has not been given the attention which it deserves. Also the other symptoms, which may be varied and vague, always include the complaint of gastrointestinal discomfort.

2. The presence of cholecystographic evidence which is almost infallible as a test of gall bladder function, especially when the dye is administered intravenously.

3. The presence upon operation of usually slight to moderate thickening, with external adhesions and evidence of a mild pericholecystitis. Also the corresponding microscopic change, including the constantly associated chronic hepatitis.

4. The immediate relief of the distressing symptoms after cholecystectomy. All of the cases have been followed up, and in every instance there has been complete relief of symptoms. This is a revelation in the 52 cases of Group D, where 34, or 65 per cent, were indefinite and where the diagnosis was made only by the cholecystogram. This was done early in the disease, before extensive scarring occurred and before marked damage to the liver had taken place. The first of this series of 100 cases has been in perfect health thirty months since operation. The last patient, operated upon ten months ago, is also free from all of her old complaints. Whether this will continue to be the case in these persons in the future remains to be seen, but for the present we are amply justified in concluding that cholecystography has fully proved its worth. Based on the patient's statements of therapeutic results, therefore, after cholecystectomy, the cholecystographic diagnosis in the most uncertain type of case clinically was 100 per cent correct. In previous articles on cholecystography from this clinic the statement has been made that this means of diagnosis has been found accurate in from 93 to 97 per cent⁹ of the cases in which the gall bladder was removed and examined microscopically. The discrepancy between these figures and the 100 per cent of accuracy just

mentioned is due to the fact that in a few cases the microscopic examination of the removed gall bladder showed no abnormality. The excellent clinical results in all of these cases, however, after cholecystectomy, seemed to corroborate the cholecystographic evidence of gall bladder disease.

Summary. 1. One hundred consecutive cases of chronic cholecystitis are reviewed in which the cholecystogram was used in the diagnosis and in which cholecystectomy was done.

2. Extensively scarred and thickened gall bladders, with or without stones, represent the end stage of a long-standing disease.

3. These can usually (70 per cent) be diagnosed by careful history and physical examination.

4. Cholecystography in these cases has been an infallible corroborative laboratory procedure.

5. Cholecystography is an index of physiologic function of the gall bladder and with this in mind cholecystitis can be detected long before marked gross changes have occurred in the gall bladder.

6. In every case so diagnosed cholecystectomy has resulted in complete relief of symptoms.

7. Chronic hepatitis is constantly associated with chronic cholecystitis, no matter how slight the latter may be.

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NONSPECIFIC GRANULOMA OF THE SMALL INTESTINE.

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THREE years ago we described¹ the pathologic and some of the clinical features of a malady which, we had reason to believe is not uncommon, and yet, as far as we are aware, was not widely known in this country. Its recognition at that time seemed to have been

confined to European observers. The literature of this subject covers but little more than the past decade, is almost entirely casuistic and concerned mostly with the clinical phases. Before this period, descriptions of this lesion were by no means uncommon under the designation of "hyperplastic tuberculosis of the intestine" or syphilis. The disease is important clinically and is a malady which both the clinician and surgeon must consider in dealing with obscure tumors in the abdominal cavity. The cause, with exceptional instances, is still unknown.

For want of a better name, the condition was called "non-specific granuloma" of the intestine. Four cases were described, all involving the colon, and one involving both colon and small intestine. The histologic characteristics were those of a simple granuloma. No evidences of tuberculosis, syphilis or lymphogranulomatosis were present, although especial attention was given to this point. The granulomata involved various portions of the colon. The infiltration of the wall may be more prominent on the mucosal or on the mesenteric sides of the bowel wall. In both instances the lumen is narrowed. Ulcerations, which are usually superficial, may be present; exceptionally, there is abscess formation. The cause has not been determined. In a few cases foreign bodies and a colitis have been reported. Clinically, these cases presented signs of constriction of the intestinal lumen and a palpable mass along some portion of the colon. The nature of the condition was not diagnostic before operation.

Another case belonging in this group of nonspecific granulomata of the intestine is reported in this communication in which the varied characteristics of the lesion are exemplified in two operative specimens removed during operations separated from one another by a period of six years. In the second of these specimens the lesion was present entirely in the small intestine in contradistinction to the location of the lesion removed at the first operation and to those reported previously by us in which the bulk of the lesion was present in the large intestine.

Case Report. A man, aged eighteen years, was admitted to the hospital with the clinical picture of an acute perforating lesion of the appendix. His family and previous history had no essential bearing on the present condition and, in fact, this was the first illness the patient had ever had. According to most careful questioning at no time was there any sign or symptom of any manifestation of a tuberculous or syphilitic infection of any part of the body.

The illness began on the day previous to admission, was ushered in with severe generalized abdominal cramps and was associated with vomiting and with an inability to move the bowels. Within a few hours after the onset, the pain localized in the right iliac fossa and fever appeared. Thereafter the symptoms progressed so that at the time of admission to the hospital they were well marked. The physical examination disclosed generalized abdominal rigidity, most marked on the right side with tenderness

limited to the right iliac fossa where a small mass was palpable. The examination of the rest of the patient's body disclosed nothing abnormal.

There seemed to be no doubt of the diagnosis of an acute appendicitis and the patient was immediately subjected to operation (Wilensky). On opening the abdomen a large inflammatory mass was seen to occupy the right iliac fossa involving the angle of junction of the ileum and ascending colon. After unravelling the mass it was determined that a much thickened, inflamed, gangrenous and perforated appendix passed upward from its usual point of origin in the ileocecal junction to the left and inward toward the median line; partly it, and partly the adjacent coils of ileum and ascending colon formed the dense walls of a small abscess containing about an ounce of grayish white pus. The abscess cavity lay partly to the right and partly to the left of the corresponding leafs of the mesentery; and the tip of the appendix projected through a communicating opening. As far as one could see there were no other evidences of further disease in the operative field. As a matter of fact, the condition resembled in every particular that seen with the ordinary forms of suppurative appendicitis. Therefore the appendix was removed in the usual way, the abscess cavity was cleaned, and, the appropriate drainage having been adequately provided, the abdominal incision was closed with the exception of that part from which the drainage apparatus emerged. It was expected that the usual post-operative course would follow and that healing would result promptly in the ordinary manner.

Much to our surprise and chagrin a fecal fistula developed at the end of the first week. The discharge was never profuse and its fecal nature disappeared within a short time. Then the wound contracted to a narrow deep channel from which an insignificant amount of purulent discharge escaped each day. Every opportunity was afforded for the closure of the wound but at the end of the fourth month practically no progress was made and it became apparent that a secondary operation would be necessary to insure the closure of the intestinal fistula and the healing of the wound.

At the second operation (Wilensky) the cause for the persistent sinus became apparent immediately. The sinus led down to a pinpoint perforation in the beginning of the ascending colon; from the latter, and extending on both sides but much more in an upward direction, a segment of colon was demarcated by an extraordinary rigidity and thickening of its walls. It was only natural to assume that the lesion was of tuberculous origin; and at the moment this assumption dictated the further operative treatment of the case. No other lesion being found, the terminal portion of the ileum, and the caput and the ascending colon as far as the hepatic flexure were excised and the continuity of the alimentary canal was reestablished by a side-to-side suture anastomosis. No drainage was employed and the abdominal wound was closed. An uneventful convalescence followed and at the end of the second week the patient was discharged from the hospital apparently well.

The specimen removed at the second operation is a very interesting one. The entire lesion lay in the ascending colon; the ileocecal valve and the small intestine was free from any evidences of disease. This corresponds with the picture described in the cases previously reported. The lesion was apparently (gross observation) distributed throughout all of the coats of the bowel; however, it seemed that the bulk of the infiltration had been attracted more to the peritoneal side of the intestinal wall. The mucous membrane showed no open ulcerations, but it was manifestly much thinner than normal,

and the thinness of its texture was altogether out of proportion to the thickening of the rest of the wall. The gross appearance of the major distribution of the infiltration toward the peritoneum was seemingly corroborated by the absence of encroachment upon the intestinal lumen and a finger passed easily in either direction through the compromised area.

The patient continued well and with no symptoms of any kind for the next five and a half years. Then very suddenly he developed abdominal pain and vomiting with an inability to evacuate either stool or gas from the bowel. There had been no indiscretion in diet and apparently no other cause sufficient to account for the reappearance of any symptoms. The latter increased in severity; at the end of the first day the patient was markedly distended; however, there was no rigidity and no special point of tenderness on the abdominal wall; the impression was distinctly given that the bulk of the trouble was in the right iliac fossa.

A high enema was given. A profuse evacuation of gas and thin liquid stool immediately followed and the abdominal distention disappeared. For a number of hours the patient was comfortable but very soon the symptoms began to reappear, to progress rapidly and to reach a stage even more severe than had existed before the enema was given. Operation (Wilensky) was therefore, determined upon in the expectation of finding either one of the ordinary forms of intestinal obstruction or, possibly, the sort of lesion being discussed in this paper. This type of lesion had been kept fresh in our minds since the publication of our previous report.

On opening the abdomen, a small amount of clear serous exudate escaped and the small intestine seemed uniformly distended. The point of obstruction was easily determined to be a fairly large mass which lay in the right iliac fossa in the region of the previous operation and which consisted of a tangle of intestinal coils in the terminal ileum just proximal to the previous ileocolic anastomosis; the mass was adherent on one side to the stump of the ascending colon. The intestinal coils which made up the mass were very much thickened and the intimacy of the adhesions between the one and the other made it certain that any attempt to disentangle them *in situ* would result in more than one opening into the intestinal lumen with a consequent outpouring of infectious contents into the peritoneal cavity. It seemed better judgment to resect the entire mass and the procedure was carried out. The adhesions were freed, the mass was lifted out of the belly, the appropriate part of the mesentery was divided between clamps, and the involved portion of the alimentary canal including the terminal ileum with the mass of adherent coils and the proximal part of the stump of the ascending colon with the new anastomosis was cut away between rubber covered clamps. One half of a Murphy button was dropped into the open end of the resulting stump of the ascending colon and the opening was closed with a double layer of sutures in the usual way. A short distance away from the suture line a small incision was made in the side of the colon and the neck of the button was pulled through. The other half of the button was fastened into the open end of the stump of the ileum. Then the two halves of the button were locked together reestablishing the continuity of the alimentary canal by an end-to-side anastomosis.

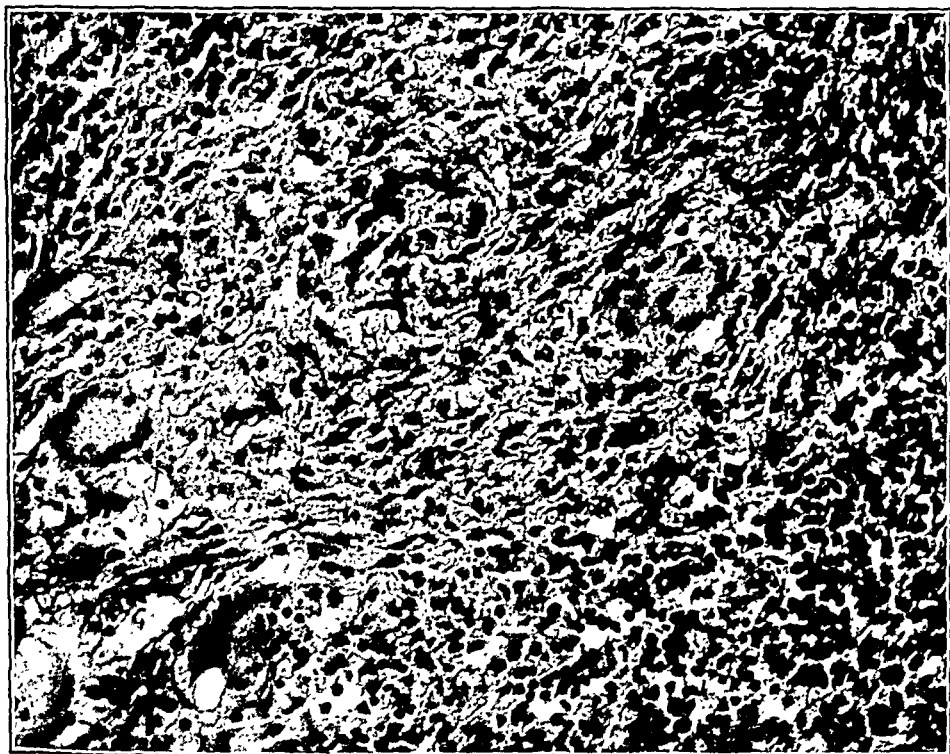
The patient did not do well after operation. Almost immediately the temperature began to rise and at the end of the first twenty-four hours it had reached over 105° F. There were the usual accompanying symptoms of a profound intoxication and death followed. The intoxication resembled those seen with severe and hyperacute forms of intestinal obstruction.

The specimen consisted of about 1 foot of terminal ileum and about 3 inches of the ascending colon together with the anastomosis made at the second operation. The anastomosis was in perfect condition. The portion of the ascending colon was normal also. It was not possible even outside the body to unravel the adherent coils, so intimate were the adhesions, so much thickened were the intestinal walls and so extensive and almost cartilaginous in consistence was the inflammatory exudate which surrounded and glued the entire mass into one. The best that one could do was to insert a blade of the scissors into the open end and to progressively open the intestinal canal as one followed its course in the convoluted mass of gut. The windings of the gut resembled the entangling of a bunch of worms. At one part and for a short distance, the thickness of the bowel wall was so marked as to encroach upon the lumen to the extent that it became difficult for the blade of the scissors to pass through; a distinct stenosis was present. The mucous membrane was thinned out and the atrophy must have been a progressive one for in places the attenuation had reached the stage of superficial ulcerations.

The amount of the inflammatory infiltration in and between the adherent coils made it somewhat difficult to determine the extent and distribution of the infiltration in the intestinal wall itself. However, in one stretch, especially—the stenotic area—it was easily distinguished that the predominance of the bowel wall thickening was in its inner layers and toward the lumen of the bowel. This was in contradistinction to the distribution of the lesion in the segment excised at the first operation in which, as has been previously said, the bulk of the infiltration was toward the peritoneal surface.

Microscopic Examination (Moschcowitz). The dominant picture is that of an extensive, diffuse, round cell infiltration of all the coats of the intestine. In some areas, the cells are so closely packed together as to resemble lymphoid bodies. There is a moderate sprinkling of multinuclear giant cells, in some of which there are clear round or oval spaces, which appear as though they had contained foreign bodies. The subperitoneal connective tissue is much thickened. On the mucosal aspect granulatous areas have formed with formation of new bloodvessels. In these granulomatous areas, there is an abundant sprinkling of polymorphonuclear cells. Scattered areas of normal mucosa are visible here and there between these granulomatous areas. In addition there are a number of small distinct abscess formations, especially on the inner aspects of the gut. There is abundant fibrinous exudate present on the mucosal side. There is also abundant fibrous tissue transformation in all the coats of the intestine (see Fig.). The microscopic picture is definitely not that of tuberculosis or syphilis.

The two specimens removed from this patient exemplified in one



High power photomicrograph of lesion in small intestine, showing morphology and arrangement of giant cells.

way or another the characteristics common to this lesion which were pointed out in our previous paper. There is a "tumor" of greater or lesser size which may involve any portion of the gut. The inflammatory process usually involves all the coats of the intestine. Sometimes the proliferation is most prominent in the inner coats which narrows the lumen of the gut. There is ulceration of the mucosa, which, as a rule, is superficial and not extensive. Adhesions to surrounding structures and to the abdominal wall are common. In a few instances, only, does the induration extend to the ileocecal valve, causing narrowing of this structure. Abscess formation is rare. The tumors reveal typical granulomatous changes in various stages of development. There is never the slightest evidence of tuberculosis, syphilis, or newgrowth, or diverticulitis.

The remarkable resemblance of some of the reported cases to hyperplastic tuberculosis of the intestine has led to a great deal of confusion. Undoubtedly many if not a majority of the cases of so-called "hyperplastic tuberculosis of the colon" are really simple granulomata, lesions that are identical in every way with those which we have reported. This case had been forgotten at the time and was not included in our first report. The report made by Dr. Mandlebaum on the second specimen removed during the third operation recalled the circumstances of the case and reflection caused a reappraisal of the pathologic condition and the belief that the case properly belongs to the group described as nonspecific granulomata of the intestine. It does not require much reflection after reading the literature on tuberculous and allied forms of intestinal infection to realize that similar errors have been and are constantly being made.

In the vast majority of the reported cases the etiology was unknown. A curious feature in all 4 cases which were reported in our first communication is a history of a previous attack of appendicitis or of a preceding appendectomy. Two of the cases had definite suppurative conditions in the appendix.

The same extraordinary association with an attack of acute appendicitis was also present in this case; the intestinal lesion followed an attack of what was apparently the ordinary variety of acute suppurative appendicitis—the kind which is always expected to go on to cure with no secondary or subsidiary phenomena to disturb the constancy and permanence of the cure, of course, with the exception of the ordinary forms of intestinal obstruction due to adhesions, and so forth.

The relationship of inflammatory lesions of the large and small intestine has repeatedly been referred to in the literature (De Ruyter, Gangitano, Lawen, Gato, Teitze, Korte). In most of these reports, however, the inflammatory process is said to be continuous with that of the appendix and involves only the contiguous portion of the cecum. From our own surgical and laboratory experience we

are prepared to say that this form of typhlitis is merely the peripheral part of the inflammatory reaction in the appendix, and entire permanent subsidence of this regularly follows concomitantly with the removal of the appendix and the healing of the focus of infection. Such secondary typhlitic conditions are quite commonly encountered in far advanced suppurative appendicular conditions. In each particular, there is a parallelism to the forms of hepatitis accompanying inflammatory conditions of the gall bladder.

We do not agree with the assumption made in some of the reported cases of primary typhlitis in which this lesion has been assumed to have caused a subsequent appendicitis. The finding of an occasional case in which the inflammatory process is distinctly limited to the wall of the cecum without involvement of the appendix—typhlitis proper—and the extreme rarity, if not absence of persistence of the above mentioned simple inflammatory lesion in the cecal wall after the appendix has been removed would make it fair to assume that the path of spread of the inflammatory lesion is from the appendix into the cecal wall, rather than that the appendix lesion should have been initiated by primary involvement in the wall of the cecum.

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FUNCTIONAL SPASMS IN CHILDREN, THEIR PHYSIOLOGIC PATHOLOGY, AND THEIR RELATION TO THE NEUROSES IN LATER LIFE.

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ONE of the principal physiologic properties of muscle tissue is contractility. This may be hypotonic, tonic, hypertonic or spasmodic. Spasms are abnormal, involuntary muscular contractions. They are usually of limited extent, involving only groups of muscles in response to localized central or peripheral nerve irritations or to general nervous dysfunctions. Spasms may be skeletal, visceral or emotional. When the striated or skeletal muscles are affected the neuromuscular disorder is easily observed and interpreted. Spasms of the nonstriated or visceral muscles, and spasmophilic emotional disorders, are difficult of observation and diagnosis.

Skeletal or External Spasms in Children. These manifest themselves mainly as carpopedal spasms or general spasmophilic con-

vulsions. In the carpopedal type there is hyperesthesia with tonic spasms of the extremities. The upper extremities are usually involved to a larger extent than the lower. As a result of a circulatory interference during the spasmodic seizure, there is often edema of the dorsal surfaces of the hands and feet. The carpopedal spasms may continue for hours, days or even weeks. General spasmophilic convulsions are first local, later becoming general. They start, usually, in the muscles of the face and spread rapidly through the entire body, with tonic spasms followed by clonic, general rigidity, cyanosis and unconsciousness. After a few minutes the spasms relax, consciousness returns and the child appears as well as ever. The spasmophilic attacks may be repeated.

Visceral or Internal Spasms in Children. Viscerospasms are of considerable diagnostic and therapeutic importance. Many ailments in childhood are due to excessive, irregular or spasmodic contractions of the internal organs. The digestive, respiratory, circulatory and urinary muscle tissues may be affected.

Spasms of the Digestive Tract. Regurgitation, rumination, vomiting, gastralgia, enteralgia, gastrointestinal hyperperistalsis, and constipation are frequently due to spasms. Regurgitation in infancy is quite common. While in many infants it is simply a welling up from the stomach of excessive food, in some cases a sudden cardiospasm sends up the food with a gush. Rumination, though rare, is seen in children of neurotic constitution. The ruminant act is probably due to irregular spasmodic contractions of the upper portion of the alimentary tube which cause direct and reversed peristaltic waves, sending the food in turns upward and downward. Esophageal spasm without gastrospasm occasionally occurs in infancy and early childhood. Vomiting without a definite pathology is not uncommon in children. Fear, excitement, distaste for school and forced feeding cause in certain children a reflex gastrospasm and vomiting. Pharyngeal irritation with reflex gastrospasm and vomiting is seen in children, giving rise to the so-called morning vomiting. Pylorospasm as a cause of vomiting is quite common in infancy. Care must be taken to differentiate pylorospasm from pylorostenosis. Gastralgia and enteralgia in infants, known as colic, are frequently present without pathologic changes or gross dietetic errors. They are evidently the result of spasmodic constrictions and dilatations of various segments of the gastrointestinal tract. Gastrointestinal hyperperistalsis is the cause of many cases of diarrhea in early infancy. Each time the baby is put to the breast or the bottle, it has one or more bowel evacuations during feeding. In the majority of cases there seems to be nothing wrong with the food or the feeding. The suckling act or the contact of milk with the gastric mucosa sends down waves of hyperperistalsis along the gastrointestinal canal which produce one or more movements. Constipation is quite common in children.

Spasms of the colon or the anal region block the normal peristaltic sweeping motions. A proper and timely diagnosis of the neuromuscular disorders of the digestive tract in infancy and childhood will prevent serious illness.

Spasms of the Respiratory System. Laryngospasm, laryngismus stridulus, spasmodic cough, bronchospasm, pneumospasm and diaphragmatic spasms are of frequent occurrence in infants and children. In laryngospasm there is usually a slight laryngitis with a spasmodic contraction of the larynx causing noisy breathing, inspiratory dyspnea and cyanosis. The attacks are mostly nocturnal and may be repeated. Laryngismus stridulus is a disease of infancy, especially of those of a rachitic or neurotic diathesis. There is a stridulous breathing more or less constant. Any exciting cause may precipitate a severe laryngeal spasm with a period of apnea. During the paroxysm the infant becomes cyanotic, throws back its head, becomes rigid and is in great distress. After some seconds the laryngeal spasm relaxes and the infant takes a deep stridulous inspiration. Spasmodic cough unassociated with any illness of the respiratory system occasionally occurs in children and is rarely properly diagnosed. The cough may be more or less continuous or paroxysmal and may last for days, weeks and even months. It is of reflex origin due to some central or peripheral irritation of the vagus or its branches. Bronchospasm in children is frequently present without bronchial asthma. It is purely a neuromuscular instability, causing spasmodic contractions of the bronchial tree with dyspnea and some sibilant rales. Quite commonly bronchospasm is an added element to catarrhal bronchitis or bronchopneumonia which causes the respiration to become more noisy, labored and wheezing. Treatment that will relieve the bronchospasm will add to the comfort of the little patient and aid in its recovery. Bronchial asthma is essentially a neuromuscular spasmodic disorder, whatever other factors may contribute to its etiology. Pneumospasm may occur in the newborn infant. The respiratory process is frequently irregular in early life and the breathing is slow, rapid or unsteady. This is probably due to an arrhythmic function of the neuromuscular system of respiration or to an oscillation of the carbon dioxid tension of the respiratory center. Spasm of the diaphragm is quite common in infants and young children, causing hiccough. Chilling of the body surface or irritation of the stomach by overfeeding in addition to a hyperphrenic activity is usually the cause of the reflex action which causes spasmodic contraction of the diaphragm and singultus. Unless these various respiratory disorders are readily recognized, they will lead to faulty diagnosis and mistreatment.

Spasms of the Circulatory System. The entire cardiovascular mechanism with its central organ and innumerable peripheral bloodvessels are under nervous control and subject to irregular

or spasmodic contractions. Disturbance in contractility may be of central or peripheral origin, general or local, cardiac or vascular. The wave of cardiac contraction may irregularly affect different parts of the heart giving rise to various arrhythmias and reduplications of the cardiac sounds. Large or small areas of bloodvessels may show sudden constriction and dilatation though not in response to the normal physiological supply and demand. Local hyperemia or anemia, pallor or blushing due to purely spasmodic vascular changes can be easily observed in children as a result of a vasomotor imbalance. A proper diagnosis of the functional circulatory disorders in children is of paramount importance.

Spasms of the Urogenital Tract. Painful spasmodic contractions of the kidneys and ureters simulating renal or ureteral colic is seen in children. One of the most common causes of enuresis and frequent urination is spasms of the urinary bladder. Uterine spasmodic contractions in female children causing pelvic pain or discomfort is not uncommon especially when nearing puberty.

Emotional Spasms in Children. The spasmophilic diathesis may be seen in children showing no definite symptoms or signs of muscular spasms. The hyperexcitability seems to be chiefly emotional. These children are precocious, impulsive, irritable, sleepless and cry easily without evident cause. They are subject to headaches, night terrors, periodic vomiting, anorexia, dirt eating and masturbation. On careful investigation there may be found some latent neuromuscular spasm or instability. But the dominant condition is that of mental unrest or emotional spasmophilia.

Spasms in children have as their etiology a physiologic pathology and not an anatomical pathology. Childhood is the age of neuromuscular imperfection and instability. The fetus in utero is an automaton, the infant is a reflex mechanism and the child is in a state of neuromuscular imbalance. The threshold of sensory nerve reaction is low, the voluntary brain centers are not fully developed, the psychic control is imperfect, and the motor nerves respond disorderly. At the basis of muscular spasms in children are a hereditary predisposition and an inexperienced, untrained, rapidly growing nervous system. When to this is added some metabolic disturbance, as a deficiency in the calcium ions or a dissociation of the acid-base balance, with a retention of bases, some infectious disease, or a malnutrition of the nervous system, local spasms or general tetany results. Hypoparathyroidism through its influence on cellular chemistry and metabolism may also cause physical or emotional spasms. The premature infant is especially prone to spasmophilia.

Diagnosis. As functional spasms are the result of an aberrant physiology and not of an abnormal anatomy, the diagnosis must be based chiefly on symptoms. Spasmophilia may manifest itself as general, carpopedal, visceral, or emotional. These spasms are

characterized by a seasonal variation, being worse in the winter; by a disordered metabolism, with a calcium content of less than 10 mg. per 100 cc. of blood serum; by a perverted neuromuscular reaction and an increased excitability to the galvanic current. The hyperexcitability of the peripheral nerves to the galvanic current is shown by a kathodal opening contraction of less than 5 milliampères or by an anodal opening contraction of less than 2 milliampères. In addition to this Erb's electrical phenomenon, the Chvostek facial nerve contraction in response to tapping along the course of the facial nerve, and the Trousseau phenomenon of tetany of the hands elicited by constriction of the arms are pathognomonic signs. Anemia and a hypochlorhydria are frequently present and are of diagnostic importance. Electrocardiography in spasmophilia gives varied results. In some cases the electrocardiogram is normal in others there are marked variations in the ventricular complex.

Spasmophilia, rachitis, status thymicolymphaticus and functional epilepsy have many points of analogy in their abnormal neuromuscular behavior. The frequent and repeated spasms, the low calcium metabolism, the Erb, Chvostek, and Trousseau signs, are indicative of spasmophilia. The slow development, the characteristic bony changes, the deficiency in calcium and phosphorus point to rachitis. A hyperplasia of the thymus and the lymphatic system, stridulous thymic breathing, lymphocytosis and a tendency to sexual abnormality are diagnostic factors in status thymicolymphaticus. The aura, nocturnal attacks, sudden convulsive seizures and the mild forms of petit mal, are all in favor of epilepsy. Spasms due to organic changes in the nervous system are evident by a history of brain or nerve injury, by spasticity or flaccidity and by a deterioration of body or mind.

The relation of spasm in children to the neuroses in later life seems to be, in many cases, a very close one. Many of the etiologic factors in the spasmophilic diathesis are conducive to a persistent disorder. The spasmophilic child is usually conceived in an unhealthy inheritance and born with an irritable nervous system. It is aggravated by a lack of breast feeding, poor general nutrition, insufficient air and sunshine, and by repeated spasmodic attacks. The nervous anomaly may persist in a recessive or a dominant form, or be converted into the various neuroses in later life, or be transmitted to a future progeny. Epilepsy, hysteria, neurasthenia, psychoasthenia and the various habit spasms may have a juvenile spasmophilia as a background. In some cases, however, the prognosis is good. As there is no anatomic nerve destruction, the nervous system gradually emerges from its state of hyperirritability and disorderly conduct.

Treatment. Treatment begins with the birth of the child. The rapidly growing nervous system should be protected by quiet,

peaceful surroundings and the best hygienic care. Breast feeding is essential, when this is not obtainable, fat-free bottle feeding should be given, with the addition of cereals, vegetables and toasted bread. On the first sign of spasms, any source of infection should be removed, the general health improved and a proper diet given. Warm baths, cod liver oil with oil of phosphorus, iron carbonate saccharated, calcium bromid, chloral hydrate, and antipyrin are indicated. The functions of the endocrine set should be investigated. Parathyroid may be tried. Ultra-violet therapy does good.

Summary. Functional spasms in children are more frequent than spasms due to organic nerve lesions.

The striated or external musculature as well as the various internal organs may be affected, giving rise to a multitude of disorders. Emotional spasmophilia may manifest itself in various abnormal actions and reactions.

An early and proper diagnosis should be made of the many obscure ailments in children which have a neuromuscular or a psychic spasmodic diathesis as their basis.

Proper food, and healthy surroundings will act as a prophylactic during infancy. Calcium salts, phosphorated cod liver oil, iron, and whatever symptomatic treatment is indicated, will do much good as a cure and also as a preventive from drifting into the neuroses of later life.

THE PERIODIC HEALTH EXAMINATION.¹

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THE medical profession has placed the stamp of approval upon the periodic health examination. This new gospel has been proclaimed throughout county, state and national organizations as one of the fundamental measures for health conservation. From the medical man, this doctrine is being passed on to the public with the able assistance of the press, both medical and lay, and through the medium of public schools, colleges and universities. The great life insurance companies have done much to further this movement.

It will not be difficult to convince the layman of the advantage to be gained by following this teaching. The arguments for a periodic health examination are logical, convincing and conclusive. We may differ somewhat in our views as to the manner in which

¹ An address delivered before the Philadelphia County Medical Society on May 26, 1926.

the examination should be conducted and as to whether it can be most advantageously made by the family physician, a medical group or an institution, but there will be little divergence of opinion as to the merits of the procedure itself.

This new relation of the physician and layman will create a new meaning for the term "patient." Webster defines "patient" as "A sufferer; one who bears or endures; a sick person." It becomes apparent at once that the patient of the future will not conform to this definition. He will demand of his physician that he be kept from playing the rôle of sufferer.

The same authority defines "physician" as "A person skilled in physic or the art of healing; one duly authorized to treat diseases." The physician of the future, in like manner, will be called upon to play a new rôle. He must now, in addition to his difficult duty of treating disease, take upon himself the far more difficult task of detecting disease in its incipency, guarding against disease tendencies and advising regarding personal hygiene. He must be skilled in the science of dietetics; he must advise regarding hours of sleep, work and rest; he will be called upon to interpret minor symptoms of obscure significance, which the patient will call to his attention; he must be informed as to the effect of occupation, climate and heredity on disease tendencies; he must be prepared to advise the patient regarding his routine of life and he must have sound judgment and scientific facts back of this advice.

If we assume that this new teaching will be accepted by the layman, it follows as a matter of course that he will request of his physician this type of service and that health examinations will be in ever increasing demand in the community.

It might be well for us at this point to take stock of our diagnostic and therapeutic armamentarium, and critically examine the means at our disposal for meeting this new demand. It would also be in order to devise a form of procedure for carrying out this type of examination. Considerable work has already been done along these lines. Various county, state and national organizations have prepared excellent forms and distributed a great deal of literature regarding health examinations.

While the difficulty of detecting disease in its incipency is well recognized, the health examiner will become increasingly proficient as he practises this type of service and we may confidently expect greater diagnostic skill and keener interpretation of so-called trivial symptoms as a result.

I know of no position in which a medical man can be placed which will demand more of his professional resources and create a more acute sense of his own limitations than to be called upon to conduct periodic health examinations. The patient appears before the examiner in a new and perhaps unfamiliar character. He is not sick; he has no complaints, or perhaps a few minor ones; in fact he

will frequently state that he is in excellent health. His one concern may be to maintain this present state of health, and yet it is a well-known fact that this very individual may, in his present so-called state of health, already have incipient disease of which he is entirely unaware.

An analysis of the present causes of death in the registration area of the United States serves to call attention to the principal diseases which the health examiner will be called upon to combat. It will be noted that diseases of the heart lead all other causes of death, with tuberculosis second, and with nephritis, malignancy and influenza and pneumonia rising and falling but always constituting an important cause of death. Separated from this group by a perceptible interval is the group consisting of diabetes and the infectious diseases, typhoid fever, diphtheria, measles, whooping cough and scarlet fever. These diseases, then, are the ones most likely to cause the death of the patient whom we are examining.

The procedure which we have followed for some years in conducting a health examination consists of three broad divisions. The first involves the history of the patient. This includes his family history, his previous health, and his present condition, together with a careful inquiry as to any symptoms, however trivial, which he may have at the present time. The second step includes the physical examination, and the third such laboratory study as may be indicated by the first two steps.

The history of the patient assumes probably more importance in the health examination than in the examination for ordinary consultation. It is surprising in how many instances the patient is unable to give us accurate data regarding his father and mother, and when inquiry is made regarding grandparents or great grandparents, the answers are frequently vague, or even misleading. The importance of these data regarding the patient's ancestors can hardly be overestimated, and in every instance an effort should be made to secure all the data possible, not only regarding parents, brothers and sisters, but also grandparents and great grandparents, as well as any information the patient may be able to furnish concerning cousins, uncles and aunts.

It often happens that while the patient is unable at the time to furnish reliable information regarding his antecedents and relatives, he is able to accumulate these data with very little effort from other members of his family, and it is urged that data be obtained in every instance where it is possible to do so.

The bearing of heredity on disease tendency is coming to assume more importance than at any time in the past history of medicine. There are several well-established familial diseases and defects, such as muscular dystrophy, defective color perception, and defective perception for variations in the pitch of sounds. The chemical

elements responsible for coagulation of the blood may be absent or feeble, so that hemophilia appears; in fact, any organ of the body may fail of normal development and may show variations in susceptibility or resistance to disease through heredity. Any light which can be thrown on the patient's susceptibility to disease through a careful study of hereditary factors will be of the greatest value to the health examiner. Not only this, but the health examiner is in the ideal position to pursue the study of hereditary factors in disease and to bring to light new data on this important phase of medicine.

The ideal method of conserving the patient's health would be by examinations at regular intervals and over a period of time, so that data accumulated over a number of years may be used to the best advantage. Consulting first one and then another health examiner means a waste of time, added expense and the unnecessary duplication of work and of important records. As these observations are continued from year to year, the advice of the health examiner becomes increasingly valuable to the patient.

The data acquired regarding a patient's previous health should be complete, accurate and include information concerning any illness or injury from childbirth to the present time. The salient points in the history should be summarized and underscored so that they may be quickly referred to in subsequent examinations. Data regarding the occurrence of any of the acute infectious diseases, particularly scarlet fever, measles, diphtheria, typhoid, pneumonia, pleurisy, tonsillitis, influenza, rheumatic fever and chorea, should be carefully sought. A careful history should also be obtained regarding diseases of the gastrointestinal tract, the circulatory system, the nervous system and the genitourinary tract.

The present condition of the patient, which really means his own opinion as to his present condition, should be carefully ascertained. While the patient's opinion of his own physical and mental state often does not reflect the true condition of affairs, it is one of the important guides of the examiner to the correct estimation of the patient's condition. Evidences of emotional instability, neurosis, apprehension and anxiety, as well as accurate data regarding the patient's mental development, intellectual qualities, and even direct leads bearing on organic disease may be obtained in this manner.

This preliminary history-taking should be a deliberate affair. Much depends upon it, and any attempt to hurry it or cut short the patient's recital of seemingly trivial symptoms may deprive the examiner of important suggestive leads. It is necessary that the patient make a confidant of the examiner, as otherwise, important data which he should be acquainted with is frequently never brought to light. This is another reason for repeated examinations over a period of time, as often it is only in this manner that the patient really unburdens himself to the examiner, who is thus enabled to regulate the patient's life with greater skill and success.

The medical history should always include a careful scrutiny of the patient's personal hygiene. Under this heading we would consider: (1) dietary habits; (2) use of alcohol and tobacco; (3) habits of sleep; (4) hours and character of work; (5) recreation and hobbies; (6) habits of exercise; (7) bathing habits; (8) regularity of bowel movements. Accurate information regarding each of these factors should be obtained and recorded.

Dietary habits include a careful summary of the patient's average daily intake of food, with as accurate an approximation as possible of the intake of fats, carbohydrates and proteins. A careful estimate of the vitamin content of the food intake should be made. The amount of salt, pepper, spices and other condiments consumed should be recorded. These data may then be used later in recommending any modifications of the patient's present diet which appear necessary from a consideration of his history and physical examination. The fluid intake should be carefully inquired into, as this information will act as a guide for certain later recommendations. The amount of tea, coffee, milk, chocolate or cocoa consumed by the patient is also included in the record.

The patient's habits in regard to alcohol and tobacco should be accurately recorded. There can be little question, no matter what one's personal opinion may be, that in certain individuals the consumption of alcohol has a deleterious effect, and in these instances its use must be curtailed or prohibited. The use of tobacco has come to be such a common practice among both sexes that we would do well to inquire carefully regarding the amount consumed by the patient. While tobacco in moderate quantities can be used by many people without untoward effects, the fact remains that not infrequently the use of tobacco results in harm to the patient, and the physician should be on the alert to detect evidences of such harmful effects. Occasionally these effects may be manifested through defects of vision or disturbances of the cardiovascular system, such as various forms of arrhythmia. Not infrequently, gastrointestinal symptoms are due to the use of tobacco, and its effect in producing spasm of the colon with resulting attacks of discomfort and pain should not be lost sight of.

In attempting to regulate the habits of the patient, however, the examiner would do well not to attempt the indiscriminate interdiction of articles of food or attempt the abrupt change of habits of a lifetime without having a good reason for such action. It is well to keep in mind that it is possible to irritate a patient by useless and petty restrictions which may do more harm than good.

Regarding the hours of sleep, work, rest and play, no hard and fast rules, applicable to all types of patients, should be attempted. Insistence on eight or nine hours daily rest in bed for one patient might be a hardship for another, and mental reaction and temperament should be taken into consideration.

It may be stated, as a general rule, that recreation or the pursuit

of a hobby should be encouraged. The patient himself is usually the best judge as to when such recreation or diversion interferes with his routine of business, but, from the standpoint of the physician, such recreation or hobby, particularly if it involves regular, daily outdoor exercise, should be encouraged.

The question of exercise demands careful consideration, particularly in view of the large number of cults and fads now in vogue, and the many special courses of exercises which are urged upon the unsuspecting layman as a panacea for all ills. It is possible to do considerable damage, particularly to patients of middle or advanced age, by exercise too violent in nature or too long continued at one time, and, particularly, by exercise indulged in occasionally and sporadically. The business man who, through stress of duties, is prohibited from indulging in his favorite pastime of golf for a week, may attempt to compensate by playing over the week-end as much as thirty-six holes of golf at one stretch, not realizing that such a procedure is likely to do him more harm than good. It should be impressed upon the patient that it is the daily, regular, mild exercise which is the safe and health-giving practice to pursue. Of the many forms of exercise recommended, none can be used with greater safety or more accurately measured than walking in the open air. This form of exercise can be prescribed for almost any type of patient who is not actually confined to his room.

The occupation of the patient should receive careful scrutiny. While the examiner does not pose as a vocational expert, nevertheless, it is clearly within his province to inform the patient if his present occupation is affecting his health adversely. He should also ascertain whether the patient's occupation is congenial or if there continually arise conflicts, which, through their depressing mental effects, impair the patient's efficiency and productiveness.

The health examiner must be careful not to confine his activity to the physical findings of the patient. He must consider as equally important his client's mental state if he would justify his position as a health examiner. The home environment of the patient should come in for careful consideration. A quiet, congenial home environment makes for physical and mental well-being; whereas, a depressing, irritating home environment has a distinctly unfavorable effect on the patient's health. It may be possible for the health examiner to improve such conditions by timely and well-considered advice. It is well for the examiner to acquaint himself with the patient's religious status, if he would round out his knowledge of the patient's psychology.

Before proceeding with the physical examination, it is in order to ascertain whether the patient has been protected against certain of the acute infectious diseases, which procedure medical science has made possible. It is the duty of the examiner to make certain that his client is protected against smallpox. The presence of an old

vaccination scar is not sufficient evidence of such protection, and a recent positive vaccination or an immune reaction should be obtained. The advisability of recommending vaccination against typhoid fever should be considered for each patient. Such vaccination is of proved value and involves practically no risk to the patient. The patient's susceptibility to diphtheria should be determined, particularly if he be of an age where such susceptibility is frequent. Determination of such susceptibility should, of course, be followed by vaccination with diphtheria toxin-antitoxin. Among the younger patients the determination of susceptibility to scarlet fever should be carried out in like manner, and the patient given the benefit of vaccination against this serious disease.

The medical history is dealt with in some detail, in order to indicate how important we consider this part of the health examination.

From this careful study of the hereditary factors bearing on susceptibility or resistance to disease, and from a careful study of the diseases or injuries which the patient has already had, the examiner is then in a favorable position to proceed with the actual physical examination. He has already obtained important leads which will place him on guard in considering the functional activity of the various organs.

The physical examination of the patient should follow some definite program, and the results of this examination should be accurately recorded and become part of the permanent record of the patient. It may follow along somewhat the usual lines and should be unhurried and thorough. The patient is weighed and his height determined and observations are made regarding figure, frame and posture. The chest is measured at inspiration and expiration, and the circumference of the abdomen ascertained.

The examiner should determine from these data whether or not the patient has the proper weight. In fact, he should come to a conclusion regarding this important item, without taking into consideration the weight as recorded by the scales.

Using the above procedure as a guide, we found in 9454 health examinations that 395, or 4.17 per cent, were definitely overweight. These individuals considered themselves in good health. It is not difficult to convince this type of patient of the advantage of gradual weight reduction.

Too often the medical man forms his opinion regarding overweight or underweight from looking at a printed table of average weights for given age and height, instead of actually examining the patient to see whether such a weight fits in correctly with the patient's body build, posture and type. The bony frame-work differs in every individual, the hereditary factors vary, and the environment of no two individuals is exactly alike. A little careful scrutiny of the patient will tell the examiner more regarding his correct weight than any set of tables or measures he could devise. The practice of

ordering an individual to reduce a given number of pounds when he appears above the average weight and when his build is such as to indicate no superfluous fat, but rather a heavy bony framework and extensive muscular development, cannot be too strongly condemned.

On the other hand, attempting to add fat to an individual with a light bony framework and slight muscular development, who enjoys excellent health, is equally futile. It should be realized that each individual comes of different ancestral stock, and any attempt to have him necessarily conform to a common standard can only result badly. In fact, if it were possible to draw up rules of life which could be followed by every individual, there would be little need for the health examiner. It is the examiner's duty to study his patient as an individual and not as a member of a group.

The examination may then be continued with a study of the special senses. The acuity of vision is determined and the question of wearing glasses or modifying those at present worn is determined. The state of the lids, the conjunctiva, cornea and pupillary reflexes are determined. An ophthalmoscopic examination of the fundus is also made, and the state of the retinal arteries determined.

The state of the hearing is determined, for which the whispered voice at fifteen feet may be used, and the external auditory canal and the ear drums are carefully examined.

The nasal cavity is examined, and the presence of deviated septum, enlarged turbinates, defective breathing space, discharge from sinuses or the presence of polypi or other abnormalities determined.

The throat is carefully examined and the state of the tonsils and tonsillar pillars inquired into. It is a simple procedure to retract the anterior pillar and make slight pressure on the tonsils, and such procedure should be carried out in order to determine the presence of infective material in the tonsillar fossæ. Reddened or inflamed tonsillar pillars are suggestive of infection, and the ability to express caseous or purulent materials from the tonsillar bed is a strong indication of tonsillar disease.

The sinuses should come in for careful inquiry and if there is anything in the history or the examination which suggests sinus infection, careful Roentgen ray plates of all sinuses should be made.

The teeth constitute an important factor in health, and it is not sufficient to pass them by with a cursory examination. The relation of focal infection to disease has been greatly stressed in recent years, and while there can be no doubt of such relationship, there is frequently a reasonable doubt as to the accuracy of methods by which the presence of such focal infection is determined. The practice of sending a patient to a Roentgen ray specialist who has no particular knowledge of dental pathology, except from a radiographic standpoint and of basing recommendations on this report alone is not

justifiable. A thorough dental examination will include the following procedures, which we place in the order of their relative importance:

1. A careful clinical examination of the teeth. This includes a search for caries; malocclusion; an examination of the state of the gums; the determination of the presence of abscess or fistula and calculus. It also includes a careful estimate of the available grinding surface, which is particularly important to health, as lack of sufficient grinding surface may be the basis of much gastrointestinal disturbance and consequent ill health.

2. A careful test of all teeth for vitality. This can be done with quickness and accuracy with an electric pulp tester.

3. Roentgen ray of all teeth. This serves to confirm evidence presented by the foregoing procedures and reveals evidence of periapical disease.

4. Transillumination. This procedure is quickly and easily carried out and serves to supplement the foregoing procedures and frequently throws added light on the state of the teeth.

We believe if these four procedures are carried out in every case that the presence of dental disease can be determined with a fair degree of accuracy and that teeth will not be needlessly sacrificed on insufficient evidence.

The examination of the cardiovascular system, in view of the importance of diseases of this system as a cause of death, should be particularly thorough. Listening to the heart sounds in the precordial region is not sufficient and the patient should receive the benefit of one of the simple cardiac functional tests. The test which we have been using consists of twenty hops on each foot at the rate of one hop a second and recording the blood pressure and pulse rate immediately before, immediately after, and three minutes after such exercise. More elaborate tests may be used such as the Schneider index or the stair-climbing test. It is important to ascertain whether the heart is carrying on its functions easily or whether the load is becoming burdensome, and whether it may be advisable to curtail the patient's activities in deference to a failing heart muscle.

The state of the bloodvessels can be determined with a fair degree of accuracy if the examination includes a study of the retinal arteries and a careful survey of the superficial arteries.

The presence of hypertension may call for special measures to safeguard the patient's future. In classifying the records of 9936 health examinations, arterial hypertension of 150 mm. of Hg or higher was found in 2.69 per cent. Individuals showing hypertension should be subjected to special tests to determine as far as possible the functional activity of the kidneys and the presence of focal infection in these patients would justify more radical procedures, perhaps, than in individuals without this finding. The

advisability of recommending special procedures such as electrocardiographic examination and orthodiagraphic studies will depend on the findings at the time of the examination.

The examination of the respiratory system would always include a careful search for evidence of early tuberculosis. While tuberculosis ranks second to cardiac disease as a cause of death, it has shown a steady decline in its mortality for many years, and it is reasonable to assume that this rate will continue to decline in coming years. In fact, it has been predicted by workers in this field that tuberculosis as a cause of death will eventually disappear entirely. The early detection of tuberculous disease offers to the patient the best chance for ultimate recovery and the health examiner must be alert and fully equipped to detect this disease in its incipency.

A careful survey of the nervous system designed to detect early evidence of neurologic disorders should be conducted. This neurological examination can be made without any elaborate equipment and the health examiner should be well versed in the early symptoms of diseases of nervous tissue.

The examination of the abdomen should be designed to detect any abnormalities of the viscera. A careful palpation is made for areas of tenderness, increased resistance and the presence of masses.

Cancer as a cause of death has shown slight but steady increase for several years and the health examiner would do well to keep this fact in mind particularly when examining patients whose age places them in a group favorable to its development. Vague and obscure digestive symptoms may be the only indication of malignancy of the gastrointestinal tract for many months and the patient's seemingly trivial symptoms should not be regarded lightly. A Roentgen ray examination of the gastrointestinal tract following a barium meal should be considered if any suspicion of serious gastrointestinal disease arises. This Roentgen ray examination should always include a study of the colon after it has been filled with a barium enema, as not infrequently early malignancy of the colon will show no evidence of its presence without a barium enema.

Special laboratory tests designed to show the functional activity of the various abdominal organs should be performed if indicated by the history or physical examination.

The genitourinary system demands special consideration. Nephritis as a cause of death holds third place, and stands as a constant challenge to the health examiner. A careful urinalysis is always indicated and the health examiner should satisfy himself that the functional activity of the kidneys is not impaired. Medical science has developed a formidable array of renal functional tests. The estimation of the blood chemistry, the phthalein test, the Mosenthal test, the water ingest test and the urea concentration test are all of distinct value and are comparatively simple procedures to carry out. The significance of albumin or of albumin and casts in the urine is

not always clear but should always serve to call attention to the kidney function and demand a thorough search for possible etiologic factors.

It is manifestly impossible in this short space to describe in its entirety the health examination. We have attempted to set forth in some measure the scope of this examination. The increasing importance of this subject can hardly be overemphasized, and the need for qualified health examiners will undoubtedly be felt with increasing force as the public sees the value of this type of service. It behooves one who would conduct health examinations to properly equip himself in this particular branch of medicine.

The importance of syphilis as a cause of ill health, invalidism and death is perhaps not sufficiently emphasized in a study of mortality statistics. It frequently happens that deaths due directly to syphilitic infection are charged up as disease of some particular organ or system and the etiologic syphilitic background lost sight of. Syphilis offers a shining mark for the health examiner. The detection of syphilis during the health examination and its subsequent adequate treatment will do much to further the interest of the patient. It follows as a matter of course that tests for syphilis will be made on all patients during the health examination and, where indication exists, that the cerebrospinal fluid will be also carefully tested. In every patient with a history of syphilis, both blood and spinal fluid should be examined so the physician may have this added information to guide him in safeguarding the patient.

Such laboratory procedures as may be indicated from a survey of the history and the results of the physical examination should be carried out in each instance, so that a modern laboratory is an essential adjunct to the equipment of the health examiner.

Summary. The medical profession is practically unanimous in approving periodic health examinations. It can be confidently predicted that the layman will accept this teaching and will demand of his physician this particular type of service.

It, therefore, follows that the profession must provide well qualified practitioners in medicine to conduct this type of examination.

In carrying out this procedure, the medical history of the patient becomes of great importance. No set questionnaire will suffice for accumulating this history and much depends upon the skill with which the examiner elicits and builds up the data he secures from the patient.

The routine of physical examination in the health examination may differ somewhat from that of the ordinary consultation and the examiner must grasp at seemingly slight or trivial leads in order to detect incipient disease.

The personal hygiene of the patient will demand closer scrutiny than it ordinarily receives from the attending physician.

A well-equipped laboratory for conducting tests to determine the

functional activity of the various organs is a requisite for the successful health examination.

Periodic health examinations over a number of years place the examiner in the ideal position to advise the patient regarding his routine of life.

This new relationship between physician and patient will tend to throw new light on the hereditary factors in disease, develop keener diagnostic ability, better functional tests and a more accurate interpretation of seemingly trivial symptoms which may herald incipient disease.

The patient is viewed from a different angle and the question is not only what is his present state of health, but also, what will it be ten or even twenty years hence.

The health examiner must chart the road map which the patient will follow in his journey through life. The hazards that lie ahead must be plainly marked, the detours indicated and the speed limit clearly understood.

THE CLINICAL VALUE OF INTRAVENOUS INJECTION OF CONGO RED IN THE DIAGNOSIS OF AMYLOID DISEASE.

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THAT dilute solutions of Congo red can be injected into the circulation without disturbance has been known for several years. It has been used in this way to determine blood volume and for other experimental purposes.¹ It was found that injected into the blood stream it becomes homogeneously distributed in the plasma in four minutes, and that it begins to disappear in ten minutes. In the normal there are no traces left in the blood at the end of twenty-four hours.

Bennhold² studied the behavior of the dye in certain pathological conditions, comparing the amount present after one hour with that after four minutes. In the normal, 11 to 30 per cent of the dye had disappeared at the end of one hour. In glomerular nephritis and nephrosclerosis (15 cases), he found normal values. In liver diseases, the disappearance of the dye was distinctly delayed. The retardation, however, was so variable that it could not be used as a functional test.

In two conditions only, he found a decided increase in the rapidity with which the dye left the blood, namely: (a) Pure tubular

nephritis (nephrosis). Two of the 4 cases were of luetic origin. All showed a disappearance of 47 per cent to 55 per cent of the dye in one hour. (b) Pulmonary tuberculosis. In 6 out of 9 cases in which amyloidosis was found postmortem, the dye disappeared with remarkable speed. Often it had left the blood at the end of one hour. Pulmonary tuberculosis without amyloid gave normal values.

He concludes that the disappearance of over 60 per cent of the dye in one hour is diagnostic of amyloid disease. Disappearance of between 40 and 60 per cent may occur in either amyloidosis or nephrosis.

The rapid disappearance of the dye from the blood stream he found³ was due to absorption by the amyloid substance and that the serum played an important part in this phenomenon. In a patient dying twenty hours after injection, the amyloid tissue was found deeply stained by the dye, and in another patient, at death five weeks following the injection, staining of the amyloid tissue was still present. Patients without amyloidosis, who had been injected shortly before death, had no deposit of the dye in the organs.²

Failure of the typical rapid disappearance of the dye he states will be evidence only against widespread amyloid, and especially against amyloid liver. Deposits in the kidneys alone have not sufficient volume to give the typical reaction.

The test has been used by Schönberger and Rosenblatt, by Paunz and by Nèmeth⁴ in small series of patients. Their results were similar to Bennhold's but no attempt at quantitative estimation was made. Paunz and Nèmeth used a slightly modified technique. Koref⁴ was able by this test to confirm the diagnosis of amyloid in a child.

Technique of the Test. Our method differs but little from that of Bennhold and is as follows:

We used a 0.75 per cent, later a 1.2 per cent solution, prepared as follows: The powdered Congo red (Grübler) is mixed with water, heated to boiling, filtered through a Berkefeld filter, and divided into hard glass ampules each containing about 15 cc. These are then sealed. The solution must contain no undissolved particles. Of the stronger solution 10 to 15 cc. are injected, according to the size of the patient, into a vein at the elbow. The needle is left in place and after four minutes 10 cc. of the blood are withdrawn. At the end of one hour a second specimen of 10 cc. is taken.

Serum (which must be free from hemoglobin), is obtained by bleeding through a dry needle into a paraffin tube which is quickly transported to the laboratory packed in ice, the blood immediately transferred to an unparaffined centrifuge tube and centrifuged at 1500 to 2000 revolutions per minute for at least 15 minutes. The fibrin is then detached from the walls with a needle, being careful not to approach within a centimeter of the red-cell zone. The clot is allowed to retract and the tube again centrifuged for five minutes.

The serum is then pipetted off and the color content of the one-hour specimen determined with any colorimeter, the four-minute specimen being used as a standard. We found the Kuttner-Leitz Universal microcolorimeter most useful for this purpose. The addition of dilute hydrochloric acid to the serum changes the color to blue. At times this was found of advantage as a check on the matching of the red color.

We have used the test in 18 patients. No disturbance resulted from the injection of the dye.

No.	Clinical classification.	Amyloidosis present clinically.	Amount of disappearance of Congo red per cent.	Enlargement of liver.
1	Chronic passive congestion of liver due to cardiac or arterial disease	No	30	4+
2	Chronic passive congestion of liver due to cardiac or arterial disease	No	35	3+
3	Chronic passive congestion of liver; chronic osteomyelitis	?	35	4+
4	Atrophic cirrhosis of liver	No	30	
5	Carcinoma of stomach; secondary carcinoma of liver	No	30	2+
6	Chronic generalized lymphangitis	No	20	
7	Nephrosis	No	54	
8	Chronic osteomyelitis	Yes	100	+
9	Chronic osteomyelitis	Yes	40	3+
10	Tuberculous osteomyelitis	Yes	100	3+
11	Tuberculous osteomyelitis	Yes	100	4+
12	Tuberculous osteomyelitis } Tuberculous peritonitis }	Yes	80	4+
13	Pulmonary abscess	?	80	
14	Chronic pulmonary tuberculosis with empyema	?	30	+
15	Advanced pulmonary tuberculosis	No	50	
16	Advanced pulmonary tuberculosis	No	50	
17	Advanced pulmonary tuberculosis	Yes	100	+
18	Advanced pulmonary tuberculosis	No	35	

NOTE: Each plus (+) indicates that the edge of the liver was felt so many fingers' breadths below the right costal margin.

Clinically we find the test of great value in the diagnosis of amyloid disease and can confirm Bennhold's results, which were controlled by pathologic examinations. In 1 of our patients, autopsy confirmed the positive result of the test.

In a number of miscellaneous conditions, with involvement of the liver but in which there was no reason to expect the presence of amyloid, the test was negative.

In a case of nephrosis we found, as did Bennhold, increased disappearance of the dye.

Of 5 patients with chronic bone suppuration, in 4 the test confirmed the clinical diagnosis of amyloid. The remaining patient is still under observation. One of these patients showed a disappear-

ance of 80 per cent (Case 12) of the dye. At autopsy, four months later, with extensive tuberculosis of the spine and other tuberculous lesions there were amyloid deposits in the liver, spleen and kidneys. The kidneys were moderately enlarged, the spleen slightly, the liver not at all. The lack of large amyloid deposits in the liver explains why the disappearance of the dye was not complete.

In a patient with pulmonary abscess, the positive response to the test helped confirm the suspicion of amyloidosis, while in 1 case of chronic pulmonary tuberculosis with long-standing empyema the normal response to the test appears confirmed by the subsequent favorable course.

Four patients with advanced pulmonary tuberculosis gave varying responses, all showing dye disappearance greater than normal.

Conclusion. Disappearance of 60 per cent or more of Congo red from the blood in one hour is found only in the presence of amyloid disease. A lower rate of disappearance does not preclude the presence of amyloidosis.

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NOTES ON SULPHATE OF EPHEDRIN.*

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THE physiologic properties of ephedrin, an active principle of the Chinese herb, *ma huang*, have been very fully reported upon by K. K. Chen and C. F. Schmidt, of Pekin, in 1924;² T. G. Miller,

* Delivered before the American Therapeutic Society on June 10, 1926.

of Philadelphia, some twelve or fifteen months later investigated the drug from the clinical standpoint.³

Over five thousand years ago the Chinese Emperor, Shen Nung, the so-called "father of Chinese agriculture," tasted and classified a large number of herbs then in common use by the Chinese apothecaries, and his book, the *Pentsao*, still serves as a reference work of drugs for Chinese physicians. There have been many editions published, the last, printed in 1596, contains a total of 1871 drugs. In the list occurs the herb *ma huang*. The Chinese still use it a great deal, chiefly as an antipyretic, a diaphoretic and as a sedative in certain respiratory diseases. An active principle, an alkaloid, was first isolated by Nagai, in 1887,¹ which he called ephedrin (the botanical name of *ma huang* being *Ephedra vulgaris*). His chief claim for it was that it acted as a decided but harmless mydriatic. Later other investigations showed that in the dog an injection of the alkaloid was followed by a rise in blood pressure and by a relaxation of intestinal muscle. In the frog it was noted that it caused cardiac depression.

Physiologic Action of Ephedrin. The first thorough and scientific investigation into the physiologic action of ephedrin was done in the Peking Union Medical College by Chen and Schmidt in 1924.² Our work followed more or less on the lines laid down by these workers and in a general way have fully confirmed what they reported. This pharmacologic investigation was done in the laboratories of the University of Toronto and we owe much to Prof. V. E. Henderson for constant advice and coöperation.

THE EFFECTS OF EPHEDRIN ON THE CIRCULATION. 1. *Blood Pressure.* The most decided effect of an intravenous injection on the circulation of the dog was an outstanding and prolonged increase in the blood pressure. In one experiment an injection of 5 mg. caused an immediate rise in blood pressure from 75 to 200 mm. This effect on the pressure, while being fairly abrupt, was not at all transient, as at the end of eleven minutes it was still maintained. An intravenous injection of 0.5 cc. of 1 to 1000 adrenalin solution to the same animal on another occasion caused a rise in blood pressure of 130 mm., but this rise was very transitory and within two minutes the pressure had fallen to its former level.

2. *Action of Ephedrin on the Heart.* Coincident with the rise in blood pressure there occurs in animals a very definite cardiac acceleration. In the above experiment the pulse rate increased from 164 to 264 beats per minute. The effect on the cat's heart was carefully studied, using the plethysmograph. Besides the increase in rate a very definite augmentation in the strength of the cardiac contractions was elicited and the tracings showed an increased excursion. In several of the experiments, however, the ephedrin, more especially when repeated, apparently exerted a harmful effect on the cardiac muscle. Numerous extrasystoles occurred, and occa-

sionally acute cardiac dilatation appeared which necessitated artificial respiration and cardiac massage before the heart's action once more became regular. We also noted that repeated doses of ephedrin would have no further effect on the blood pressure and cardiac rate. Especially was this the case when the initial dosage had been large. Apparently repeated doses will act only until a certain arbitrary level has been reached, this level varying in different animals, and after that no further increase occurs, and, in fact, in some instances a fall of pressure may result.

Chen and Schmidt showed by a series of careful experiments that apparently the action of ephedrin on the heart is due to three factors: (a) Stimulation of the accelerator ganglia; (b) stimulation of the accelerator endings; (c) in some cases a direct depression of the heart muscle.

3. *Bloodvessels.* In order to investigate the effect of ephedrin on the bloodvessels a series of experiments were done with curves to show the blood pressure, the limb volume and the intestinal volume.

An intravenous dose of ephedrin in these experiments showed, as was expected, a very definite rise in the blood pressure. Coincident with the initial rise in pressure occurred a slight increase in limb and intestinal volume; but as the pressure continued to rise or remained at a high level the volume of the limb and of the intestine underwent a gradual and definite shrinkage. The probable explanation of the initial increase in volume is that it is due to increased bloodflow resulting from the increased blood pressure. Then as time goes on a sufficient degree of vasoconstriction sets in to overcome the effects of the increased blood pressure, and we find a resulting shrinkage of the limb and intestine volume. Thus it seems that ephedrin causes vasoconstriction and we noted that it was greater in the intestinal vessels than in the limbs.

Thus the action of ephedrin on the circulation of experimental animals is as follows: A sharp and prolonged rise in blood pressure, lasting some ten times as long as does that produced by adrenalin. This rise is accompanied by cardiac acceleration, increase in the force and amplitude of the cardiac systole, and by a vasoconstriction, most marked in the splanchnic area. In some cases large doses of the drug causes cardiac irregularity of the nature of extrasystoles and occasionally acute cardiac dilatation.

4. *Smooth Muscle.* The only investigation undertaken on smooth muscle tissue was into the action of ephedrin on the isolated rabbit's intestine when this was immersed in Ringer's solution at a constant temperature of 38° C. It was found that ephedrin relaxes smooth muscle only when given in relatively strong solutions as compared with adrenalin. For example, in one experiment adrenalin solution of 1 to 800,000 caused an immediate and complete relaxation with no signs of intestinal contractions, whereas ephedrin solution of the same strength caused only a slight diminution in the height of

the contractions, and even this effect was transitory. Chen and Schmidt state that ephedrin stimulates the smooth muscle of the uterus, and relaxes that of the bronchi, being analogous, therefore, to adrenalin in its effects on smooth muscle.

5. *Influence of Ephedrin on Salivary Flow.* Our experiments upon this point gave no definite results, although Chen and Schmidt reported that ephedrin causes an increased flow of saliva where atropin has been previously given.

6. *Local Effect on Mucous Membranes.* The effect of ephedrin solutions when applied locally to mucous membranes was investigated, using the nasal mucosa and following a technique laid down by Copeland.

The frontal sinus of the dog was opened into by means of a trephine and a short piece of threaded brass tubing was screwed into the trephine opening. Rubber tubing connected this with a Mariotte flask containing Ringer's solution kept at body temperature. The fluid was allowed to run into the sinus and to trickle thence into the nasal cavity, and its rate of flow was then recorded by the drops that fell from the anterior nares onto a drop recorder. When the normal had been established the tube was clamped and 5 mg. of ephedrin in 5 cc. of Ringer's solution at body temperature was injected into the rubber tubing and allowed to remain in the sinus and nasal cavity for fifteen minutes. Then the clamp was removed from the tubing and the rate of flow being the same as before, the effect of the ephedrin was determined. We found that the rate of dropping from the nares was increased on the average about 14 per cent, so apparently ephedrin solution applied to the mucous membrane has, like adrenalin, a shrinking effect, and we found that in this respect it was superior to adrenalin.

Thus ephedrin, like adrenalin, when locally applied, relaxes the smooth muscle of the intestine, and causes vasoconstriction when applied to mucous membrane.

Clinical Results. We began by using ephedrin given by mouth. The patients were all in the hospital and were confined to bed during the morning of testing. The cases chosen were ones showing a blood pressure subnormal for their age and weight and ones only who were glad to coöperate in an intelligent manner with the investigators. No case of cardiac decompensation was used as it did not seem safe to throw any strain on an already failing heart by considerably raising the blood pressure.

As Chen and Schmidt have shown that the lethal dose of ephedrin in laboratory animals is from thirty-five to one hundred times that required to produce the full physiologic effects, our patients were given the drug with comparative freedom.

We usually gave it in a single dose of from 50 to 100 mg. The alkaloid was made into solution so that 50 mg. were contained in 1 dram of the solution. As ephedrin is very stable and does not

deteriorate when standing in solution or when exposed to light, a large amount of the solution can be made up at one time without destroying the efficiency of the drug. It is interesting to note that it is not destroyed by prolonged boiling.

All our work was done in the forenoon. The drug was usually given about 8.30 A.M., and the patient was kept under observation until the noon hour. The pulse rate and blood pressure were taken before the administration, and then every twenty minutes for the first hour and a half and then every three-quarters of an hour for the rest of the period.

(a) *Oral Administration.* All of the patients who were given ephedrin by mouth showed a rise in blood pressure, the smallest increase being 6 mm. of mercury and the largest 56. In a series of 17 patients over 80 per cent showed a rise of more than 20 mm of mercury. The diastolic blood pressures were not affected to any extent.

The ephedrin action always commenced within half an hour of administration, and the maximum effect usually appeared about three-quarters of an hour after the taking of the drug. The action was prolonged as practically all the cases still showed some increase in systolic pressure two hours later, and in some instances this was still present three and four hours afterward.

The pulse rate was carefully noted, and, with the exception of 3 cases, it dropped as the pressure rose, and then gradually rose to its former level as the effects of the ephedrin wore off.

Apparently ephedrin acts differently in the human subject and in laboratory animals in this respect, as in the latter there is always a rise in the rate of the heart, while in the former there is a fall. Miller explains this discrepancy by the suggestion that in animals under anesthesia there is a removal of vagal tone giving an increased heart rate, while in the human subject where the vagus is intact this does not occur.

In all our patients the pulse remained regular and with increased volume and force. Apparently the amplitude of the heart beat increased as the patients often remarked on precordial throbbing, and the apical impulse was often evidently accentuated.

Urinary secretion: Some 10 patients were used in estimating any effect that ephedrin might have on the kidney output. These patients received no breakfast on the morning of the test. They were given 100 cc. of water every hour, commencing at 7 A.M., up until noon. Hourly specimens of urine were obtained from 8 A.M. until 1 P.M. The ephedrin was given after the 9 o'clock specimen had been obtained. Our results were entirely useless as far as drawing any conclusion in regard to ephedrin being a diuretic, but more important was our finding that in no case did the examination of any specimen of urine suggest that the ephedrin had any irritating effect on the kidney.

(b) *Subcutaneous Administration.* When the drug was given subcutaneously and in the same dosage as *per os* the effects appeared a little earlier but otherwise were the same and lasted as long. In 4 cases where ephedrin was so administered the average rise in systolic pressure was 41 mm. of mercury.

(c) *Intravenous Use.* When given intravenously the action of ephedrin is very rapid and a much smaller dose is required to get the effects. The action of ephedrin in controlling the fall of blood pressure that so often occurs in spinal anesthesia is of special interest and as far as we know has not previously been studied. Such fall is often alarming and many efforts have been made to avert it. Babcock,⁶ of Philadelphia, uses for this purpose a solution of adrenalin in normal saline. This is given when the patient's pressure has fallen to between 30 to 50 systolic, and enough is given to keep the pressure in the neighborhood of 100 mm. for the rest of the operation. In some cases it was necessary to inject intravenously before the operation was concluded as much as 80 to 90 min. of adrenalin solution.

We studied the effects of ephedrin in 26 such cases, most of whom were operated upon by Drs. R. W. Wesley and A. I. Willinsky. The operations were for the usual conditions found in the surgical and gynecologic wards of a general hospital, and in none of them was the so-called high spinal anesthesia employed.

The pulse rate and blood pressure were determined immediately prior to injecting the anesthetic and from then on every two or three minutes until the operation was concluded.

With the first few cases we allowed the blood pressure to drop until it had apparently reached its lowest level and then 50 to 100 mg. of ephedrin were given intravenously. With but one exception there quickly resulted an extraordinary and prolonged rise in blood pressure, with a slowed and stronger heart beat. Chart I is a typical example of one of these earlier cases.

In the majority of instances one injection was sufficient to keep the blood pressure at a slightly higher level than it had been before the spinal injection for one to one and a half hours. The average increase in the blood pressure of the 26 cases of spinal anesthesia patients was 68 mm. of mercury, the lowest being 18 and the greatest 142 mm.

To show the extraordinary results sometimes obtained the case where the rise was 142 mm. may be given in some detail (Chart II). The patient a man, aged sixty-six years, was undergoing a suprapubic cystotomy. His systolic blood pressure was 170 mm. before the injection of the anesthetic. Within three minutes it was 58 mm. and the patient was in very poor condition. His color was ashy gray, respirations shallow, pupils dilated, pulse rapid and thready, and he was covered with a clammy sweat and began to vomit. One hundred milligrams of ephedrin were at once given intravenously,

and as soon as the blood pressure could be taken it was found to be 158 and soon reached 200 mm., and the whole condition of the patient rapidly improved. The pressure then gradually fell but half an hour later it was still 168 mm., or only two points below

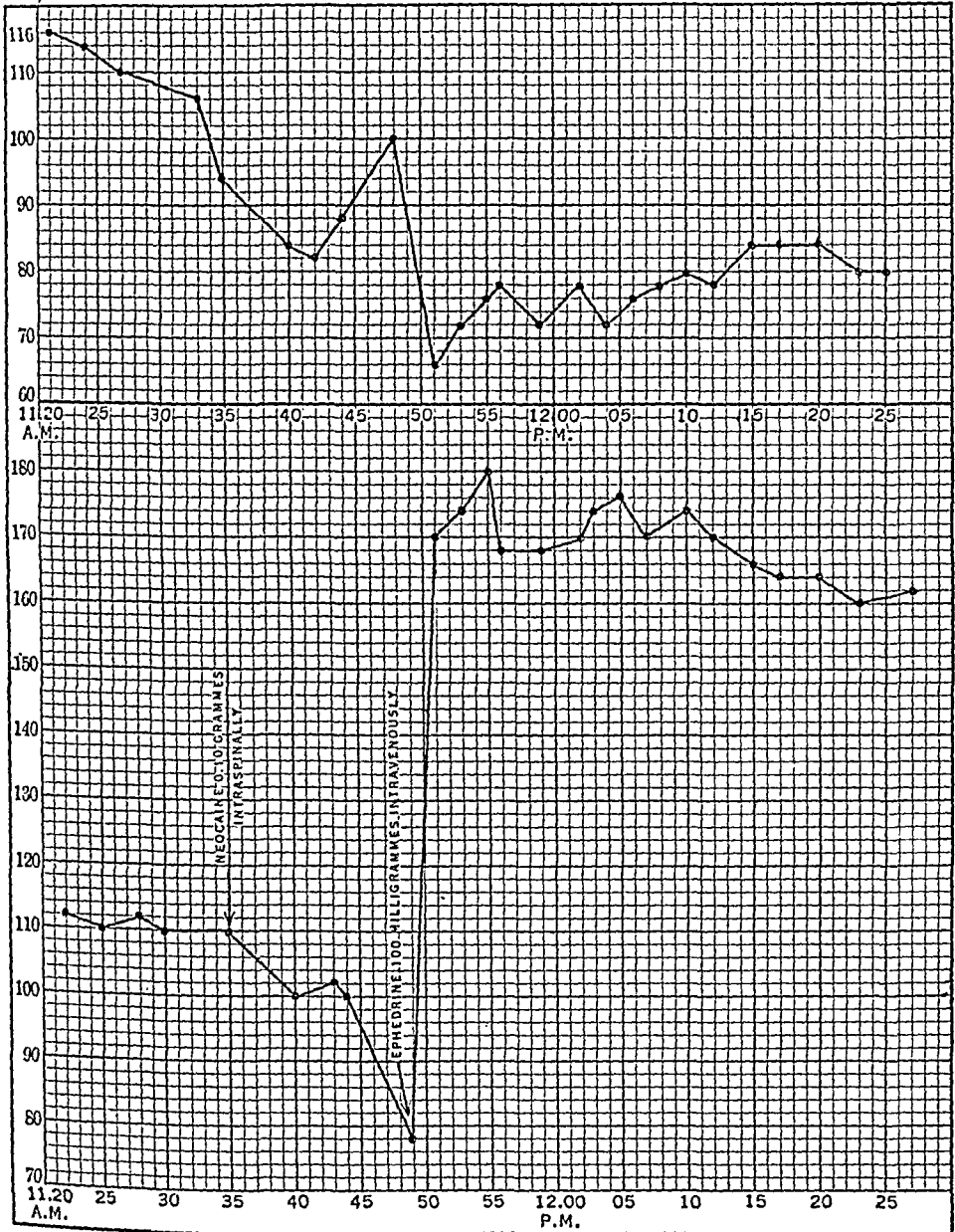


CHART I.—Upper tracing is pulse rate, lower is systolic blood pressure.

its pre-anesthetic level. The operation was soon completed and the patient did well.

Following this case we decided to employ smaller doses and to give the ephedrin within two or three minutes after the anesthetic,

so as to *anticipate* the fall of pressure, rather than to combat it after it had developed. This improved technique proved to be a satisfactory one and we failed to have any case of drastic fall in blood pressure and in no case was there any vomiting.

Ephedrin can sometimes with advantage be given before the spinal anesthetic where the blood pressure is already too low.

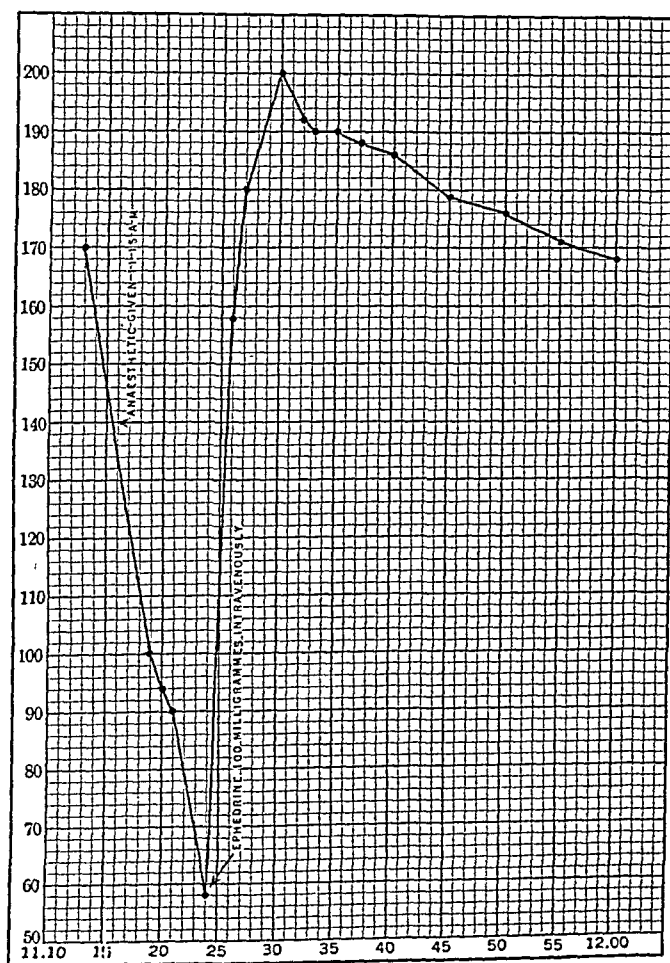


CHART II.—Systolic blood pressure.

Babcock mentions 110 mm. as the lowest limit of systolic pressure where it is safe to use spinal anesthesia. In one of our cases the man had a systolic pressure of 88, more or less ruling him out as a fit subject for spinal anesthesia. Five minutes before using this he was given 50 mg. of ephedrin and soon the pressure rose to 154 and he was then given the anesthetic. It was necessary to repeat the ephedrin later in the operation and his pressure was thus maintained above 110 mm. throughout the séance (Chart III).

It thus seems that in ephedrin we now possess a substance which will successfully prevent or combat the fall in blood pressure that so often causes anxiety during the use of spinal anesthesia.

In cases of surgical shock ephedrin may be of value. In one postoperative case, dying of peritonitis, the radial pulse could not be felt and, of course, the blood pressure was unrecordable. She was given 100 mg. of ephedrin intravenously and within two minutes the systolic pressure was 86 and the pulse could easily be counted at the wrist and was 130. The good effect lasted for some forty-five minutes and then she gradually sank and died some five hours later. Unfortunately no more ephedrin was available at the time or the result might have been very different. Chen⁸ has demonstrated the value of ephedrin in combating experimental shock in dogs.

Special Effects of Ephedrin. (a) *Influence on the Sugar Content of the Blood.* Adrenalin is known to cause a rise in the blood sugar,

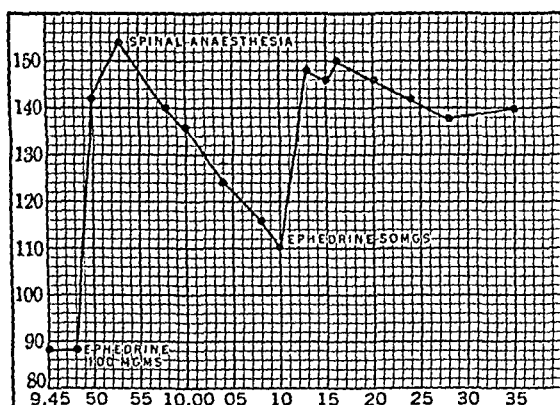


CHART III.—Systolic blood pressure

and we endeavored to find whether ephedrin had a similar effect. A series of 7 patients were used, 5 non-diabetic and 2 diabetic. No breakfast was given on the mornings of the observations. The patients were kept in bed. The first blood-sugar specimens were taken at 8.30 A.M. At 9 A.M. they each received 100 mg. of ephedrin by mouth. Nothing else was given by mouth except an occasional sip of water. The second blood specimen was taken at 11.30 A.M. Of the 5 non-diabetics 1 showed absolutely no change in the blood-sugar level. The other 4 gave increases of 7, 7, 21 and 35 mg. of sugar per 100 cc. of blood.

The two diabetics used gave varying results. The first showed blood readings of 251 mg. before and 300 mg. after the ephedrin. The second showed 250 mg. before and also after the drug.

It is apparent that much more work is necessary before one can conclude that ephedrin raises the blood sugar, but as far as these experiments go they suggest that it often has some such influence.

(b) *Effects of Ephedrin on the Respiratory Tract.* Chen and Schmidt showed that ephedrin had some relaxing effect upon the bronchial musculature, and Miller later reported⁴ a series of cases of asthma that appeared to be benefited by its use. We were only able to try it on 2 cases of this disease on account of our limited supply of the drug. Both were severe cases and each was given during a paroxysm a hypodermic injection containing 50 mg. of ephedrin. This was followed by the same dose *per os* four times daily. Neither patient showed any immediate improvement following the initial dose. One patient, however, noticed a very considerable lessening of his condition after three days of ephedrin therapy, and instead of requiring adrenalin five or six times in the twenty-four hours, could get along with only one or two adrenalin injections daily. The other man showed practically no improvement.

(c) *Local Effect of Ephedrin on the Nasal Mucous Membrane.* This investigation was carried out in the Ear, Nose and Throat Department of the Toronto General Hospital under Prof. P. G. Goldsmith. It was found that a 5 per cent solution of ephedrin when applied locally to the nasal mucous membrane caused some pallor which was not so great as after adrenalin but lasted very much longer. There were no unpleasant sequelæ.

Summary. 1. Ephedrin raises the blood pressure and slows and strengthens the heart beat.

2. On this account it should be of value in many conditions where the blood pressure is too low.

3. Especially it is shown to be very useful in preventing or combating the fall in blood pressure that is apt to be caused by spinal anesthesia.

4. There is some evidence that it tends to relieve asthma and that it raises the blood sugar.

5. All the above effects are produced by the drug when it is given by the mouth, subcutaneously or intravenously, the difference in results being only one of degree.

6. When a solution of ephedrin is applied locally to mucous membranes a blanching and shrinking effect results without any distressing sequelæ.

7. Thus ephedrin has very much the same action as has adrenalin but these effects are much more lasting, and, moreover, are produced when the drug is given *per os*.

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A NOTE ON AMPHORIC BREATHING.

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THE presence of amphoric breathing in pneumothorax is an accepted clinical phenomenon. Several theories have been proposed to account for its audition. According to one theory, the high tension under which the air is contained in the pleural cavity is responsible.

The following case report does not bear out this hypothesis, however, and proves that even a markedly positive intrapleural gaseous pressure may fail to yield amphoric breathing.

CASE I.—History, No. 8393. Right lung normal. Left lung artificial pneumothorax. Two-thirds of the lung is collapsed. Many adhesions radiating toward the periphery. Effusion at the base. The patient is receiving fortnightly refills.

REFILL ON SEPTEMBER 22, 1926.

Amount of air.	Inspiratory pressure.	Expiratory pressure.
0 cc.	-16	-8
200 cc.	-3	+3
350 cc.	+1	+10
400 cc.	+10	+20

There was no amphoric breathing heard, neither before, during nor after the experiment.

According to another theory, adhesions extending from the collapsed lung to the chest wall is the causative factor. Dr. M. Fishberg cites the following case: "Metallic breath sounds and tinkle were distinct. But suddenly the patient went into collapse with dyspnea, cyanosis, tachycardia, cold extremities, etc. Coincident with the collapse, which was evidently due to the rupture of an adhesion, all sounds in the chest, audible a few minutes before, disappeared." From this he concludes that a severance of the adhesion caused abolition of the amphoric breathing because the sound conduction from the partially collapsed lung to the chest wall was interrupted. However, the adherents of the theory that the air when in a certain condition of tension is responsible for amphoric breathing may not accept this suggestion, emphasizing that the laceration of the adhesion created a change in the air tension of the pleural cavity. Yet, we see from Case I that in spite of adhesions, in spite of an increase in intrapleural pressure, amphoric breathing was absent, throughout the experiment. Neither of these theories explains the origin of the amphoric sounds.

According to another assumption, amphoric breathing indicates

a perforation in the visceral pleura of the collapsed lung; but in our institution there have been and still are several patients with artificial pneumothorax evidently without an opening in the visceral pleura, yet with amphoric breathing.

I am citing the appended case:

CASE II.—*History No. 8395.* Weekly insufflations into the right pleural space give an increasing pressure as measured by a water manometer, corresponding to the increase of insufflated air.

SEPTEMBER 2, 1926.

Amount of air.	Inspiratory pressure.	Expiratory pressure.
0 cc.	-7	0
100 cc.	-6	+2
200 cc.	-6	+3
300 cc.	-5	+4

Amphoric breathing heard before and after insufflation by two observers.

SEPTEMBER 24, 1926.

Amount of air.	Inspiratory pressure.	Expiratory pressure.
0 cc.	-8	0
100 cc.	-11	+6
200 cc.	-7	+5
300 cc.	-6	+6
350 cc.	-6	+8

Amphoric breathing heard before and after insufflation by two observers.

It is evident that a fistulous opening would not permit a regular increase in pressure as noted above; on the contrary, air would escape by way of this opening and thus upward through the trachea.

On the other hand, were this a case of a valvular opening, each inspiratory effort would entrap continuously small amounts of air, so that the intrapleural pressure would be markedly positive in contradistinction to the negative pressure obtained in our cases, before refills. In addition, this case, and practically all our cases of artificial pneumothorax lacked the subjective symptoms of respiratory distress which a valvular fistula would give rise to.

In individuals with a good lung collapse there will often be heard breath sounds which do not have an amphoric quality; more often no breath sounds at all are audible; also in several instances a refill causes the original amphoric breathing to disappear. Hence, we must seek for a plausible reason to explain why the sounds emitted by the collapsed lung at times assume an amphoric quality; and at other times, do not. The only hypothesis which apparently reconciles the contradictory clinical observations is the one offered by Skoda, his being based on the physics of sound.

With each phase of breathing, the collapsed lung produces a conglomeration of faint tones. The air column within the pleural space (or within a large intrapulmonary cavity), together with its

boundaries forms a resonator (Skoda). That is to say, it is a vibrating body which selects certain tones, amplifies them and changes their quality by production of additional overtones.

In each instance of amphoric breathing heard over a collapsed lung, there occurs a selective response of resonance. The air column amplifies those particular notes contained among the breath sounds which are qualified to impress us as amphoric. To have this selective power, the air column must possess a certain height and width. The vibration of adhesions in a sympathetic wave with the air column may be a concomitant factor, being based on the same physical laws of resonance.

The fundamental conception that the resonating system must have a certain height and width so as to select certain tones from the conglomeration of breath sounds, accounts for the variability of amphoric breathing in the same patient. Any condition which will alter the height and width of the air column in the pleural cavity may impair or improve its properties as a resonator; likewise any interference with adhesions, such as tension, tearing, or lacerations, would alter the resonating system.

It must be emphasized, moreover, that the source of tones to be resonated, is also very variable. The collapsed lung must be in a certain condition of vibration so as to emanate the deep fundamental note and the high overtones which constitute amphoric breathing. Everyone is more or less familiar with the following very common observation: a trunk of a tree when pecked at by a woodpecker will convey to the ear of the listener a loud wooden sound; however, this same tree when used as a telegraph pole will vibrate sympathetically with the wires and emit a musical, bell-like sound.

Furthermore, the amphoric quality of breathing may in many instances be traced back to additional overtones produced by the insufflated pleural space. It is a well-known fact that there is a difference in timbre between tones of the same pitch produced by two violins. And so each instance of amphoric breathing in pneumothorax will depend on the emission from the collapsed lung of a certain faint fundamental note blended with overtones and on the momentary aptitude of the gaseous content of the pleural space to select and amplify them and produce additional overtones.

The difficulty of experimental proof lies in the following: A slight modification in the air content of the pleural space either before or after insufflation will change the height and width of the resonating system in variable and noncomputable proportions.

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END RESULTS OF CANCER CASES AND THE FACTORS DETERMINING THEM.*

BY ROBERT B. GREENOUGH, M.D.,

BOSTON.

CANCER is a subject which is assuming more importance year by year, as one after another of the more readily controllable diseases is brought within the scope of prevention or cure by modern scientific methods.

Whether we believe, as do many good authorities, that the steadily rising death rate from cancer can be explained by increased accuracy of diagnosis, or by the attainment of a larger proportion of population to the so-called "cancer" ages; or whether, as is maintained by other and equally good authorities, we consider that the peculiar conditions of modern existence provide opportunity for an actual increase in the incidence of cancer among our population, is after all of slight significance. No one who is concerned with the practice of medicine and surgery in this country needs any argument to convince him that the cancer problem is one of the great problems of modern scientific medicine.

It has become the custom to speak of cancer as a disease like tuberculosis, manifesting itself, as does tuberculosis, in many different organs or regions of the human body, but essentially the same in all its different situations. Nothing could be more erroneous than this view. Cancer is not a single disease. It is a whole group of diseases, varying not only in its situation in the human body, but in its form, its rapidity of growth and of dissemination, its susceptibility to therapeutic measures and its typical course as well. It is perhaps for this reason that such varying observations and opinions are recorded by competent observers in regard to the characteristic symptoms, the diagnosis, the appropriate treatment and the end results of treatment in cancer of different portions of the body.

It was the surgeon who first attempted the radical cure of cancer, and it was the surgeon who first established the fact that time alone was capable of determining the success or failure of efforts to cure this disease. At first a three-year period of freedom from disease was set up as an arbitrary limit for the reporting of cases, but it soon developed that "late recurrence" of the disease, especially in cancer of certain organs, such as cancer of the breast, might develop as late as fifteen or twenty years after operation. It is generally believed that such cases of late recurrence are due to metastatic foci of disease, established prior to operation, but on such infertile soil, or at least under such unfavorable conditions, that the cells of the metastasis are hemmed in and encapsulated,

* Read before the Post-Graduate Assembly, Cleveland, October 18, 1926

so that their growth is for a long time prevented and only under conditions arising later in the existence of the individual are these barriers or conditions altered to such an extent as to permit the further development of the latent focus of disease.

As a result of these conditions an arbitrary period of *five* years has now been generally accepted as the minimum lapse of time for reporting as "cures" or "successful" cases patients who have been operated on or otherwise treated for the radical cure of cancer; and even with a five-year period, we must make a mental reservation with regard to cases of cancer of the breast and of some other types of malignant disease that recurrence after five years, though unusual may yet take place.

The clinical diagnosis of cancer in each of its many situations demands the exclusion of a certain number of nonmalignant diseases which vary with the different organs affected; but the ultimate and final diagnosis depends always upon the pathologic picture or the tissue removed. It is for this reason that in any series of end results reported we have a right to demand the pathologic confirmation of the diagnosis in every case recorded as a "cure." These two conditions, a five-year period of observation and the pathologic proof of the diagnosis of cancer, are the criteria established by a committee of the American College of Surgeons and they are widely accepted in the surgical world, but far too many reports of the results of treatment of cancer are still published in the literature that do not fulfill these requirements and are thus of very little value.

For the purposes of this discussion we will assume that we are in agreement as to the nature of the cancer process, namely, that the disease is local in its origin, that after a longer or shorter period it extends and involves more and more of the adjoining tissues; that it spreads through the lymph channels to affect the regional lymph nodes, and that ultimately, by way of the bloodvessels and by other routes it produces more distant metastases which sooner or later cause the patient's death by interference with some vital function. While the above conditions vary enormously with different types of disease, as for instance carcinoma and sarcoma, and while the extension of disease is greatly influenced by the anatomic conditions of the point of origin, the above statement represents in general the view of the disease which is most widely accepted.

With these general considerations in mind we may then proceed to examine the factors which are operative in determining the end results of treatment, and for this study I have chosen cancer of the breast as a type of cancer which is familiar to most practising physicians. The four factors to which we may give special consideration are as follows:

1. Delay in obtaining treatment on the part of the patient and on the part of the physician.

2. Extent of disease.
3. Treatment employed.
4. The pathology of the disease.

1. *Delay in Obtaining Treatment.* The most recent figures from the Massachusetts General Hospital show that the amount of time elapsing from the patient's first discovery of a breast tumor to her first consultation with a physician averages six months; that the time elapsed from the physicians first examination to the time of operation is one and a half months, making a total of seven and a half months' delay in obtaining adequate treatment. These figures show some improvement over similar figures for an earlier period (Simmons and Daland^{1, 2}), and undoubtedly indicate that the campaign of education which has been carried on for the past ten years by organizations, such as the American Society for the Control of Cancer and by local, State and Federal health officers, is yielding important results, but they also indicate very clearly that more can be done in this direction, both as regards the education of the public and of the medical profession as well.

So far as the individual case is concerned, every day and every week of delay is of importance as we are quite unable to determine the exact moment when the disease first extends from its local point of origin by regional metastasis, but there can be little doubt that a delay of seven and a half months gives all too much opportunity for this to occur, and that the period should be shortened from seven and a half months to seven and a half weeks, or less if we are to obtain the best results from our present methods of treatment.

We must emphasize, however, that the mere duration of the disease expressed in months is of less significance than the extent to which the disease has spread during these months, because the differences in the rapidity of growth of different tumors is one of the extraordinary features of this disease. As a matter of fact there were more successful cases among those with an average duration of *over* seven and a half months in this series than there were in the cases in which the delay was less than the average. This apparent paradox, however, is readily explained when we come later to the consideration of the pathology of the disease.

2. *Extent of Disease.* The accepted measure of the extent of cancer of the breast is the condition of the axillary lymph nodes. This is not an accurate measure in every case, as it occasionally happens that tumors in the upper and inner hemispheres may extend to the supraclavicular or mediastinal nodes before they affect the axillary ones, and in other cases blood-borne metastases in the bones and elsewhere may occur early in the disease. A small focus of axillary disease may also escape the attention of the pathologist unless great care is used and a multitude of sections are examined. In general, however, axillary involvement is accepted as the most practical method of determining the degree of extent of cancer of the breast.

The percentage of five-year "cures" in cases operated upon in which the axillary nodes are proved by pathologic examination *not* to be diseased, vary from approximately 70 per cent in most of our American clinics to as high as 91 per cent in some recent figures from the British Ministry of Health. In the more advanced cases, where the axillary nodes are involved, the percentage of "cures" at once falls off to 20 to 30 per cent, or even lower, a clear indication of the importance of early diagnosis and treatment if we are to employ our present resources in the way of treatment to the best advantage. In this connection it may be permissible to quote the profound truth enunciated by Dr. Janet Lane Claypon that "It must be remembered that every late case of cancer was at one time an early one." It is only by passing beyond this early stage, without adequate treatment, that the case becomes a late and hopeless one.

Apart from the significance of axillary involvement, other manifestations of the extent of the disease must also be considered; not perhaps of so much importance in the early case, but of great importance in the selection of appropriate treatment in later and more advanced cases. I refer especially to extension to the chest and to the bones. The lungs, pleura, mediastinum, and the bony skeleton are so frequently affected in advanced breast cancer that a careful physical and Roentgen ray examination of the chest and of the skeleton is essential to the primary examination of every case, and should be repeated periodically during the follow-up period. In this way many useless and unnecessary attempts at radical cure will be prevented and appropriate radiation treatment can be supplied at a stage of the disease when it can do some good.

3. *Treatment.* There are only two methods of treatment for cancer of the breast which hold the confidence of the medical world, surgery and radiation, and it is universally admitted that treatment by radical surgical operation is the only method which can be relied upon to cure the disease. Cures by radiation without surgery are not to be expected, although radiation treatment may be combined with surgery, and in almost every case is of the greatest value in palliative treatment.

The radical or complete operation for cancer of the breast is practically standardized in our best clinics at the present time, and consists of the removal in one piece, and with a minimum of trauma, of the whole breast, all of the skin over it, the pectoralis major and minor muscles, the axillary contents and the deep fascia from clavicle to epigastrium and from sternum to latissimus. Anything short of this is an incomplete operation and fails to give the patient the chance to which she is entitled, of being permanently cured of her disease. Statistics are available from many sources to support the assertion that the radical operation gives a vastly greater number of cures than does the incomplete. In the series of cases from the

Massachusetts General Hospital, but 1 of 16 cases subjected to incomplete operation was alive and well at the end of three years.

In spite of these facts which have been well established, it is astonishing how many operations for cancer of the breast are performed by surgeons, even those in our larger hospitals, which fall far short of the so-called radical or complete operation. Of 127 cases of breast cancer which came to the Huntington Hospital in three years, 8 were operable, 34 were unoperated and inoperable, 55 were recurrent after a complete operation and 30 were recurrences after incomplete or inadequate operation in other hospitals. Thus more than a half of these cases had failed to receive proper treatment at a stage of the disease when cure could have been expected.

We must not lose sight of the fact that the earlier the patient presents herself for examination the greater the difficulty of making a positive diagnosis of cancer. The typical case with a tumor adherent to the skin, and enlarged axillary nodes is already far beyond the favorable stage for cure by operation. The specialist may make a shrewd guess in the earlier and less distinctive cases, but such a guess is not sufficiently reliable to permit a decision in which the life of an individual is concerned. It demands the confirmation of a pathologic examination, and this must be obtained by an exploratory operation. There is sufficient evidence available to justify the statement that an exploration properly conducted is safer for the patient than is the alternative of waiting for the development of more positive and distinctive signs of cancer when the possibility of operative cure will be to that extent, diminished. Such exploratory operations must be done at one sitting, with full preparation for the complete radical operation if it should prove to be required, and with a pathologist available for frozen-section diagnosis if it should be necessary. With this technique, explorations were performed at the Massachusetts General Hospital as far back as 1911, and the patients then operated upon are now alive and well.

Variations in the technical details of operative methods need not confuse the main issue. It matters little whether the operation be done with the scalpel or with one of the more recent instruments for cauterization, endothermy or electrocoagulation. My own preference is strongly for the scalpel. The value of preoperative and postoperative prophylactic radiation, however, is at present a matter of much discussion. Preoperative radiation is given with the purpose of damaging the tumor cells so that they may be less able to survive if they should be dislodged during operative procedures, or transplanted in the wound. Postoperative prophylactic radiation is given with two purposes in view—to retard or prevent the development of any tumor cells remaining after operation and to enhance the resistance of the surrounding body tissues to the subsequent development of any metastatic or recurrent nodule of tumor tissue.

The value of these two measures is at least debatable, and for lack of sufficiently reliable data still remains a matter of opinion rather than of fact. My own opinion as regards their use in cancer of the breast is as follows: A preoperative dose of Roentgen ray sufficient to do material damage to cancer cells cannot be given without serious effects upon the skin and subcutaneous tissue, as a result of which wound healing is much affected. In such cases sepsis and sloughing of the wound occurs more frequently than in nonradiated cases. Furthermore, in our experience at the Massachusetts General Hospital no greater percentage of cures is obtained, local recurrence is not diminished and the progress of the disease in unsuccessful cases is not retarded by the use of preoperative radiation. This is not altogether in accord with the observation of others (Lee), and we are at present carrying on another series of cases with preoperative radiation, but we must wait another five years for the results. So far as postoperative prophylactic radiation goes, however, we have abandoned it in all cases where, at the close of operation, there is not direct evidence that cancer tissue remains in the wound beyond the limits of surgical removal.

The employment of Roentgen ray or radium for the treatment of recurrent or inoperable cases is quite another story. We have abundant evidence that under radiotherapy such cases live longer and more comfortably than those which do not have it, and the earlier such treatment can be begun the better the results. In a series of the more favorable of such recurrent or inoperable cases at the Huntington Hospital an average of nearly a year and a half in added length of life for each patient was obtained by radiation.

The use of radiation in direct combination with surgery also offers a field for further development in the treatment of advanced cases. The decortication method of Beck, to permit direct radiation of the tumor tissue, and the open operation on the maxillary antrum combined with radium implantation (Greene) are examples of what may be done in this direction and undoubtedly influence the end results in certain restricted types of disease.

4. *Pathology.* Differences in the degree of malignancy of different tumors have long been recognized by pathologists in individual cases, but this information rarely reached the surgeon, and was not controlled by study of end results. Broders,^{5, 6} of the Mayo Clinic, in 1921, published a series of cases of cancer of the lip in which he attempted to classify the cases according to their pathologic evidence of malignancy and to check these observations against the clinical results. The clinical results and the pathologic classification agreed. Since Broders' first communication others have made similar studies and confirmed his findings; not only as regards squamous-cell cancer of the lip⁷ and external skin, but also cancer of the tongue (Simmons⁸), cervix (Martzloff³), fundus (Mahle⁴), and so forth. The classification depends chiefly upon the degree to which

the cancer cells have lost their characteristic differentiation (for function) and taken on more active growth. The term anaplasia was long ago suggested by von Hanseemann to express this idea; but it must be noted that for each different type of epithelium a different set of criteria must be established, depending upon the differentiation for function which is normal to the cell of origin.

I have myself been interested to apply these considerations to cancer of the breast. In this case we are dealing with a gland which is intended to secrete mucoid material, and the factors which determine the malignancy therefore depend upon the loss of secretory function either in the cell itself or in the architecture of the group of cells which normally should form a gland tubule. The size and uniformity of cells and of nuclei is also of significance, and the frequency of mitoses and especially of irregular and hyperchromatic forms is to be considered.

A series of 73 cases of breast cancer were studied from the Massachusetts General Hospital⁹ in all of which the end results had been determined. Without knowledge of these end results, however, the microscopic slides of these cases were studied and classified by Dr. C. C. Simmons, Dr. J. H. Wright and by myself. Only three classes were distinguished—high, low and medium malignancy. The data were then brought together, and with the following results (Greenough²).

	Number.	Cures.	Per cent.
Cases classed as low malignancy	19	13	68
Cases in medium class	33	11	33
Cases classed as high malignancy	21	0	0

From these figures we may draw the conclusion that a certain number of cases of cancer of the breast (say 25 to 30 per cent) are of so highly malignant a character that even in the early stages of the disease our present methods of treatment are insufficient to cope with them. When we admit this, however, we admit also that 70 to 75 per cent of all cases *are* amenable to cure by our present methods. At present we obtain five-year cures in only from 15 to 20 per cent of all cases of breast cancer which apply for treatment at our larger hospitals. There appears to be no good reason why this number should not be increased about fourfold.

In order to avoid confusion I have confined this discussion to cancer of the breast, but I fully believe that these same principles apply equally to many other forms of accessible and operable cancer, and that the possibility exists of greatly increasing the number of cures, even with our present methods, if only these general principles can be put in operation. To obtain these results, however, a very different attitude toward cancer must be adopted by the public and by the medical profession. We must learn that the disease is not so hopeless as has been too frequently maintained. We cannot sit idly by and wait for the discovery of some hypothet-

ical parasite or for the production of an effective antitoxin. Many of us believe that such an event may never take place. Cancer exists, however, and is destroying our adult population at a frightful and increasing rate. With our present resources alone some 70 to 80 per cent of cases of accessible cancer can be cured, and we now fail to cure more than a quarter of that number. It seems to me that the time has come for us to apply to the cancer problem the same general principles of common sense we would apply to any problem of modern life and to make an effort to do the best we can, with the resources already at our command.

Summary. The end results of the treatment of cancer are determined by the following factors:

1. *Delay.* There must be no delay on the part of the patient in seeking advice immediately upon the discovery of symptoms which are even suggestive of cancer, such as a lump, a sore, an abnormal discharge of blood or any unexplained discomfort.

There must be no delay on the part of the physician consulted in obtaining an immediate diagnosis either by examination, by consultation or if necessary by exploratory operation.

Both of these sources of delay may be done away with by education and by the provision of adequate facilities for consultation and for treatment.

2. *Extent of Disease.* With our present resources, surgery and radiation, the early local case of cancer can be cured; but the late and extended case cannot be cured, although palliative treatment of great value to the patient can be given.

3. *Treatment.* The end results in the treatment of cancer depend largely upon the effectiveness of the treatment employed. With the exception of a few situations, such as cancer of the external skin and of the cervix of the uterus, surgery is the method of choice.

The surgical treatment of cancer in most of its common manifestations has been standardized, and depends partly upon the anatomy of the region affected, and partly upon the mode of extension of the particular variety of cancer present. The complete or radical operation is the method which yields the greatest number of cures and should be performed even in the earliest and most favorable types of the disease. Incomplete operations do not give to the patient the chance of cure to which he is entitled.

Surgery may further be supplemented by preoperative and post-operative radiation, although the final decision as to the value of these measures has not yet been established.

For advanced cases, unsuited to attempts at radical cure, radiation therapy with Roentgen ray and with radium, occasionally supplemented by surgery, prolongs life and mitigates the distressing symptoms of the disease to an extent unequalled by any other treatment at present available.

4. Cancer is not a single disease but many diseases, differing not

only in location but in rapidity of growth and of dissemination as well. There are a certain number of cases which are so malignant and so rapid in their development that our present methods are insufficient to cope with them. The majority of cases of accessible cancer, however, are curable by methods of treatment now available in most of our modern hospitals, if only these methods can be applied in the early and favorable stages of the disease.

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REVIEWS.

THE PEAKS OF MEDICAL HISTORY. By C. L. DANA, A.M., M.D., LL.D., Professor of Nervous Diseases, Cornell University Medical College. Pp. 105; 56 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, \$3.00.

IN order to emphasize the high spots in the evolution of medicine, the author has chosen six peaks of medical history—Hippocrates, Alexandrian School, Galen, Renaissance, Harvey and Jenner. Leaving aside the diagram on page 14, which looks more like four peaks and four valleys, one might question some aspects of this particular selection, especially as by stopping almost a century ago, it perforce omits perhaps the greatest peak of the lot, on which we—*fortunati*—are still climbing. One can hardly expect in a book of this size even passing mention of many historical facts or that it will contain any serious additions to the accumulated knowledge of the subject. To those, however, who are perhaps making their first acquaintance with medical history, such a book gives a desirable emphasis to important periods, with hope of supplying the necessary stimulus to become acquainted later with the gaps between. The illustrations are copious and well chosen, and the bibliographic notes valuable to those who have not Garrison's fuller tabulation at hand. The author's vigorous and entertaining style is exemplified in his final statement, with which we heartily agree: "Whoever knows well the writings of William Osler is an educated man."

E. K.

OBSTETRICS. By JOHN S. FAIRBAIRN, Obstetric Physician, St. Thomas' Hospital; Lecturer on Midwifery, St. Thomas' Hospital Medical School. Pp. 221; 29 illustrations. New York: Oxford University Press, American Branch, 1926. Price, \$1.75.

THIS volume is one of a series of medical handbooks whose purpose is to deal shortly with the fundamental principles which underlie their subjects. It gives excellent concise descriptions of the physiology and pathology of reproduction and of pregnancy and labor, both normal and abnormal. A very brief chapter on obstetric operations gives but one paragraph to a description of "internal version," and another chapter gives instructions for the

management of the puerperium. Two chapters of little value to the American reader are found at the beginning and end of the book dealing with the registration and control of English midwives.

L. F.

A GUIDE FOR DIABETICS. By WALTER R. CAMPBELL, M.A., M.D., Department of Medicine, University of Toronto and Toronto General Hospital; and MAMIE T. PORTER, B.Sc., Dietitian, Toronto General Hospital. Pp. 259; 1 illustration. Baltimore: The Williams & Wilkins Co., 1926. Price, \$2.50.

THIS brief work differs from other diabetic handbooks chiefly in the extensive exposition of diabetic recipes and tables of food equivalents. The purpose of the latter is to simplify for the diabetic the substitution of a variety of equivalent foods for those of his standard diet, and thus eliminate one of the chief curses of the diabetic's dietary régime—monotony.

J. A.

DISEASES OF CHILDREN: A SHORT INTRODUCTION TO THEIR STUDY. By HECTOR CHARLES CAMERON, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Physician in Charge of the Department for the Diseases of Children, Guy's Hospital. Pp. 199. New York: Oxford University Press, American Branch, 1926. Price, \$1.75.

A POCKET-SIZE book covering a few of the disorders of childhood after the manner of Still. The reviewer sees the book as a series of lectures on selected topics rather than as a manual of pediatrics. It has the author's behavioristic theories and the readability of the British authors, enough to recommend it as being interesting.

J. S.

CLINICAL PEDIATRICS. By JOHN LOVETT MORSE, A.M., M.D., Professor of Pediatrics, Emeritus, Harvard Medical School; Consulting Physician at the Children's, Infants' and Floating Hospitals, Boston. Pp. 848; 180 illustrations and 34 tables. Philadelphia and London: W. B. Saunders Company, 1926. Price, \$9.00.

A ONE-VOLUME textbook of pediatrics, in which the subject matter is accurately and adequately covered without unduly expansive discussion. All of the recent advances in pediatrics have been included, such as the newer ideas of the etiology of rickets, measles prophylaxis and scarlet-fever prophylaxis and serotherapy. The

author, disdaining the quest for simplification in infant feeding, continues to recommend the top-milk mixtures with their mathematical intricacies as being the most physiologic feeding method. Also he disapproves of the early feeding of cereals and vegetables which most authorities favor. The book is orderly arranged and clearly printed, but would benefit by having better photographs. It can be highly recommended to the student as a textbook and to the practitioner as a desk volume.

J. S.

NEPHRITIS. By HERMAN ELWYN, M.D., Assisting Visiting Physician, Gouverneur Hospital, New York City. Pp. 347; 2 illustrations. New York: The Macmillan Company, 1926. Price, \$5.00.

AN excellent exposition of present-day views on nephritis. In many ways perhaps the best available today. In no other volume in English are Volhard's views so clearly and adequately presented. It is a valuable work for the practitioner and also for the medical student who finds the subject of nephritis as a rule so extremely difficult to understand. A minor criticism concerns the phrasing of a sentence on page 2 which reads "When water is withheld from the organism the kidneys respond by preventing water from being eliminated." This sounds like the old vitalistic doctrine, whereas it is more likely than when water is withheld from the organism the physicochemical state of the blood becomes such that no water is eliminated by the kidneys. It is a subtle but important difference. On the whole, the book is excellently written in a most clear and lucid style. The tables are clearly arranged; the references to the literature are full and satisfactory. Especially valuable are the descriptions of the various types of manifestations so often thrown together under the heading of uremia, the discussion of lipoid nephrosis and the emphasis on renal arteriosclerosis.

O. P.

HAY FEVER AND ASTHMA. By RAY M. BALYEAT, A.M., M.D., Instructor in Medicine in the University of Oklahoma Medical School. Pp. 198; 27 illustrations. Philadelphia: F. A. Davis Company, 1926. Price, \$2.00.

A STATEMENT of the subject in words of one syllable for the patient, with an attempt at the same time to give a résumé of the subject for the practitioner. The hay-fever section is quite well done.

R. K.

AMERICAN RELIEF ADMINISTRATION BULLETIN: AMERICAN MEDICAL AND SANITARY RELIEF IN THE RUSSIAN FAMINE, 1921-1923. By HENRY BEEUWKES, M.D., Medical Director, American Relief Administration, Russian Unit. Series 2, No. 45, April, 1926. Pp. 128; 101 illustrations and 9 charts. New York: American Relief Administration, 1926.

A STIRRING recital of the terrible health conditions that followed in the wake of Russia's disorganization after the World War, and the part played by the American Medical and Sanitary Relief. The opening chapter, an outline of the development of medical practice in Russia from its earliest beginnings down to the present Soviet régime, gives the reader the historical and scientific background. Then follow detailed descriptions of sanitary conditions, food conditions and the various epidemic diseases that prevailed; the program, plan and scope of medical relief as carried out by the American Relief Administration. A truly remarkable record of human suffering and achievement. R. K.

PSYCHOANALYSIS FOR NORMAL PEOPLE. By GERALDINE COSTER, Principal of Wychwood School, Oxford. Pp. 230; 4 illustrations. New York: Oxford University Press, American Branch, 1926. Price, \$0.85.

AN effort is made in this little book to bring the much involved subject of psychoanalysis within the mental reach of the average reader, and with considerable success. It is, of course, questionable whether one should attempt to make a "best seller" out of a predominantly psychiatric subject. The reviewer could well see where a book of this sort might be "prescribed" for a patient undergoing psychoanalytic treatment. N. W.

BOOKS RECEIVED.

The Life and Time of Adolf Kussmaul. By THEODORE H. BAST, PH.D. Pp. 131, 5 illustrations. New York: Paul B. Hoeber, Inc., 1927. Price, \$1.50. (To be reviewed later.)

Introduction to Physiological Chemistry. By MEYER BODANSKY, PH.D. Pp. 440, 40 illustrations. New York: John Wiley & Sons, Inc., 1927. Price, \$4.00. (To be reviewed later.)

The Treatment of Chronic Deafness. By GEORGE C. CATHCART, M.A., M.D. Pp. 88, 1 illustration. New York: Oxford University Press American Branch, 1926. Price, \$1.35. (To be reviewed later.)

Die peripherischen Lähmungen. By PROF. DR. TOBY COHN. Pp. 320, 64 illustrations. Berlin: Urban and Schwarzenberg, 1927. An expansion of a similar treatise the *Spezielle Pathologie und Therapie* of Kraus and Brugsch.

The Treatment of the Acute Abdomen. By ZACHARY COPE. Pp. 238, 146 illustrations. New York: Oxford University Press, American Branch, 1927. Price, \$3.50. (To be reviewed later.)

Self-care for the Diabetic. By J. J. CONYBEARE, M.C., M.D. (OXON.) F.R.C.P. (LOND.). Pp. 70. New York: Oxford University Press, American Branch, 1927. Price, \$1.15. (To be reviewed later.)

Muscular Contraction. By J. F. FULTON, B.Sc. (HARVARD), M.A., Ph.D. (OXON.). Pp. 608, illustrated. Baltimore: Williams & Wilkins Company, 1927. Price, \$10.00. (To be reviewed later.)

Action and Uses of the Salicylates and Cinchophen in Medicine. By P. J. HANZLIK, M.D. Pp. 200, 12 illustrations. Baltimore: Williams & Wilkins Company, 1927. Price, \$3.50. (To be reviewed later.)

Technique in the Management of Diabetic Patients. By HENRY J. JOHN, M.A., M.D. Pp. 62, 28 illustrations. Cleveland: The William Feather Company, 1927. Useful details on how to secure a proper blood specimen, and the preparation and administration of glucose and insulin.

Die Behandlung der Gonorrhöe des Mannes. By DR. PAUL ORLOWSKI. Pp. 194, 48 illustrations. Leipzig: Curt Kabitzsch, 1927.

The Specialties in General Practice. By FRANCIS W. PALFREY. Pp. 748. Philadelphia: W. B. Saunders Company, 1927. Price, \$6.50. (To be reviewed later.)

Reports of the St. Andrews (James Mackenzie) Institute for Clinical Research. Vol. III. Pp. 227, illustrated. New York: Oxford University Press, American Branch, 1927. Price, \$3.00. Eighteen articles containing the excellent published work of this Institute.

The Conquest of Disease. By THURMAN B. RICE. Pp. 363, 62 illustrations. New York: The Macmillan Company, 1927. Price, \$4.50. (To be reviewed later.)

A Manual of Pharmacology. By TORALD SOLLMAN. 3d edition. Pp. 1184. Philadelphia: W. B. Saunders Company, 1927. Price, \$7.50. (To be reviewed later.)

Surgical Clinics of North America, December, 1926. New Jersey Number. Pp. 318, 93 illustrations. Philadelphia: W. B. Saunders Company, 1926.

Chronic Rheumatic Diseases. By F. G. THOMSON, M.A. (CANTAB.), M.D., F.R.C.P. (LOND.), and R. G. GORDON, M.D., D.Sc., M.R.C.P. (EDIN.). Pp. 202. New York: Oxford University Press, American Branch, 1927. Price, \$2.75. (To be reviewed later.)

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

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Primary Carcinoma of the Thymus.—LEMANN and SMITH (*Arch. Int. Med.*, 1926, 38, 807) describe the seventeenth case of primary carcinoma of the thymus recorded in literature. The report is accompanied by a detailed clinical history and pathologic study. The diagnosis of the condition was not suspected until the appearance of metastases in the back and the discovery by the Roentgen ray of a shadow on the thorax. The authors point out that thoracic neoplasms should be considered when there is roentgenographic evidence of mediastinal change.

Hyperthyroidism, Myxedema and Diabetes.—It is only in the Mayo Clinic that it would be possible in this country to find so many cases of diabetes associated with states of hyperthyroidism as are recorded by WILDER (*Arch. Int. Med.*, 1926, 36, 736). Thirty-eight cases are studied and reported upon. Exophthalmic goiter occurs in about 25 per cent of these cases and adenomatous goiter with hyperthyroidism in about 75 per cent. Attention is called to the fact that the symptoms of one condition may obscure the symptoms of the other, particularly in the cases of severe acidosis. Mild diabetes may become severe when hyperthyroid states intervene, and severe overaction of the thyroid gland may be sufficient to induce coma in a diabetic patient. The insulin requirement is markedly increased by hyperthyroid conditions. Removal of the thyroid gland is followed by a marked increase in the carbohydrate tolerance of the diabetic who suffers from hyperthyroidism. Patients who are operated upon should be watched with extreme care, as there is danger of provoking hypoglycemic shock as a result of overdoses of insulin. This coma may be differentiated from other collapse conditions by the occurrence of a marked decrease in blood pressure. The last paragraph of the author's article is sufficiently

succinct and lucid to bear repetition: "The phenomena exhibited by patients with diabetes combined with states of hyperthyroidism or hypothyroidism may be related to the general metabolic rate, and thus may be explained without recourse to speculation as to a specific interdependence of thyroid and pancreas. It would seem that at lower metabolic rates the tissue cell is capable of utilizing a given amount of glucose with less insulin, and that with higher metabolic rates the requirement of insulin is disproportionately increased."

A Clinical Study of Congenital Heart Disease in Childhood.—A study of 100 cases of congenital heart disease by IRVINE-JONES (*Am. Heart J.*, 1926, 2, 121) brings out some interesting facts and data. The symptoms in most of the author's cases were the usual symptoms associated with congenital heart disease. Cyanosis was present in a large number of cases, to be exact in 70. Murmurs were present in nearly all of these little patients. Underweight, deficient mental development, and dwarfism were present in a very large number. Dyspnea is also a symptom of importance and pallor is present in about 25 per cent of the cases. Of particular value seems to be the finding of a large number of physical anomalies of congenital origin which are present in so many of these cases of cardiac disease. Over half of the children showed congenital defects and 24 of these patients showed multiple anomalies. This finding is of importance because it has been generally conceded, and the usual explanation given for congenital heart disease is that it is due to arrested growth and fetal endocarditis. The large number of patients who showed these physical anomalies would indicate very definitely that defect of the germ cell is the responsible factor in producing the lesions rather than intrauterine inflammation of the endocardium. Aside from the subjective and objective signs, which develop on physical examination, the author states that the electrocardiogram is practically always abnormal. Various alterations in the electrocardiogram occur, most frequent of which is right axis deviation in 75 per cent of the cases. An abnormally large Q-R-S complex was found in 45 per cent. Other variations were not as frequently discoverable. Another note worthy of observation is the strange association of albuminuria with a rapidly fatal outcome. There was no explanation given by the author for this phenomenon. Another phase of the study of more than usual interest was the frequency with which severe cyanosis was found to be compatible with an excellent prognosis, an observation contrary to the usually accepted idea that the severe prognosis bears a direct relationship to the severity of the cyanosis.

Incidence of Rheumatic Heart Disease among Diabetic Patients.—A very interesting observation has been made by BARACH (*Am. Heart J.*, 1926, 2, 196), who finds that the incidence of rheumatic fever is the same among the diabetic as among the nondiabetic, but, strange to say, in 37 diabetics who gave a history of acute rheumatic fever only 1 case of rheumatic heart disease was discovered. The anticipated number of cases of valvular disease in the general run of the population following this infection would be 18 or 19. The explanation that the author gives seems rather indefinite. He explains this finding on the basis that individuals with hereditary constitutional defects tend to certain diseases, with immunity to others and their complications.

SURGERY

UNDER THE CHARGE OF

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Repair Processes in Wounds of Tendons and in Tendon Grafts.—GARLOCH (*Ann. Surg.*, 1927, 85, 92) states that after the operation of tenorrhaphy, using the technique outlined in this paper and previous publications, repair of the tendon proceeds along definite lines, both as regards the time element and the gross and histologic pictures. It is safe to institute active motion on the fifth postoperative day and to remove the retentive apparatus on the eighteenth postoperative day, after which the repair will have proceeded to a point where the scar can withstand considerable stress and strain. Free tendon grafts inserted to bridge a defect in a tendon live as such. It is safe to institute active motion after the insertion of a free tendon graft in about the tenth postoperative day and to dispense with the retention apparatus on about the twenty-fifth day. The return of function following a tenorrhaphy or the insertion of a free tendon graft is dependent upon an intact suture line, a return of its muscle belly to a normal state and the breaking away of the tendon from its surrounding tendon sheath. The last of these three factors is the most important, and the final outcome may not be evident until a period of three or four months has elapsed.

The Pathogenesis of Biliary Calculi.—MENTZER (*Arch. Surg.*, 1927, 14, 14) states that there are probably two types and two sources of gall stone formation: (1) The bilirubin calcium stone, containing little or no cholesterol and arising within the intrahepatic ducts; (2) the cholesterol stone, containing varying degrees of cholesterol and arising within the gall bladder cavity. Disturbance of cholesterol metabolism of the body generally or of the gall bladder wall locally, with a resultant increase in the cholesterol content of bile, is probably a primary factor in the formation of gall stones. Stasis of bile and infection of the gall bladder are not essential to gall stone formation, but both are usually present with all stones. Nuclei of some sort are invariably present, and are possibly essential to the actual formation of stones. Without a nucleus it is possible that the ingredients of stones pass out of the gall bladder.

Adenoma of the Thyroid.—PARSONS (*Ann. Surg.*, 1927, 85, 107) says that there are two main types in respect to form—the diffuse adenomatosis, described by Goetsch and Eke, and the circumscribed with single or multiple encapsulated masses. The encapsulated adeno-

mata, possessing distinct vagaries as to form, have been classified as fetal or adult colloid, or cystic or calcified. These growths arise from the so-called interstitial cells. The natural history of the cells of adenomata, whether circumscribed or diffuse, is the same as that of the cells of the gland itself. Almost no adenomas are born toxic. Many achieve it and some seem to have it thrust upon them by injudicious iodine administration. Many individuals carry inactive masses throughout life. A large number, usually in the late thirties, begin to have symptoms of hyperthyroidism, often without any noticeable change in their goiter. Early operation is essential, while iodine should be avoided in adult cases. Pemberton's technique should be used for intrathoracic goiter. Encapsulation is of more value in diagnosis than the microscopic appearance.

The Mode of Origin of Gall Bladder Lesions.—DENTON (*Arch. Surg.*, 1927, 14, 1) claims that the recognition of mechanical and circulatory effects is important because they are evidence of cholelithiasis and entrance of stones in the duct system. It has not been possible to demonstrate in this series of cases lesions that were primarily of bacterial origin. Other factors than bacterial are necessary for the explanation of some of the commonly observed lesions of the gall bladder. If primarily infectious lesions of the gall bladder occur they must be uncommon. Lesions of the gall bladder should be regarded as bacterial in origin after demonstration of the causative organism in the lesion a fair number of times. The terms, acute, subacute and chronic cholecystitis, are undesirable because they carry the implication of infectious origin and cannot be correlated with clinical conditions. Pathologic states of the gall bladder should be described in morphologic terms, as edema and hemorrhage, hematoma, partial infarction, complete infarction, edematous cicatrix and cicatrix. The presence of gall stones in a gall bladder is not necessarily accompanied by pathologic changes in the gall bladder. In this series of cases approximately two-thirds of the stone-bearing gall bladders had definite pathologic changes.

Contribution to the Study of Toxic Absorption from the Intestinal Tract in Experimental High Obstruction.—BRAEYE (*Bull. Johns Hopkins Hosp.*, 1927, 40, 33) writes that the contents of a closed loop in the upper part of the intestinal tract of a dog, when injected intravenously into another animal, produce symptoms quite similar to those observed in high intestinal obstruction. Experimental work would seem to justify one in regarding the intestinal wall as a membrane conforming in some respects to the physical laws of diffusion and osmosis. In the presented experiments an attempt was made to influence the passage of toxins obtained from an obstructed bowel through the wall of an isolated loop of intestine. It was found that under the conditions of these experiments a 1 per cent solution of soap did not influence appreciably the passage of the toxin through the intestinal wall. A similar experiment made with bile added to the intestinal toxin in the proportion of 1 to 10 leads to the same conclusion, namely, that the diffusion is not materially influenced by the presence of bile.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

AND

SAMUEL W. LAMBERT, Jr., M.D.,

NEW YORK.

Clinical Effects of Lead in the Treatment of Malignant Disease.—CUNNINGHAM (*Brit. Med. J.*, 1926, ii, 931) states the results of 227 cases of inoperable neoplasm treated by colloidal lead at the Liverpool Cancer Research Organization. Cases selected for treatment were those presenting a reasonable chance of benefit which at the same time were likely to withstand the toxic effects of the therapeutic agent employed. Contraindications were gross pathologic lesions of one or more important organs of the body, serious cachexia and the idiosyncrasy of the individual. Complete examinations of the blood and renal function were made before treatment was commenced. The toxic effects of lead were observed on the blood and blood forming organs, gastrointestinal system, kidneys, liver and, to a lesser extent, on the central nervous system. In the blood all types of anemia were noted, the most common being the type in which the reduction of hemoglobin is more marked than the reduction in the number of red corpuscles. There was also noted polychromasia, anisocytosis, poikilocytosis, stippling of the red cells and nucleated reds. With such marked blood destruction all the symptoms of anemia might be observed. Anemia was treated by intramuscular injections of iron arsenite and transfusion when necessary. Recovery was more rapid from the anemia produced by large injections than from that caused by small injections repeated over a longer period of time. Gastrointestinal symptoms were a blue line on the gums, nausea and vomiting, intestinal colic, constipation and diarrhea. The "lead line" was of rather rare occurrence. Occasionally nausea and vomiting was immediate and was thought to be due to an anaphylactic phenomenon associated with the proteins in the preparation of lead, but usually it was delayed for a few days, even up to a week. With the vomiting a ketosis often developed and was benefited by insulin and glucose. Intestinal colic was a delayed symptom and morphin and atropin had to be resorted to usually. Diarrhea and constipation were unimportant. Kidney symptoms often appeared early in the treatment, and recovery from these was more rapid in cases treated by large doses than in those given smaller ones repeated over a longer period of time. Diminution in urinary output usually preceded albuminuria, which was present in 23 per cent of the cases. There was no change in blood pressure or blood urea worthy of note. Two cases died of renal failure associated with tubular necrosis. In all cases, to diminish the work of the kidney, a light, low protein diet was given with 2 to 3 pints of imperial drink and barley water daily. Temporary cessation of treatment always fol-

lowed the appearance of renal symptoms and a previous severe nephritis was a contraindication to treatment. Headache, rigors, nausea and vomiting were due possibly to impairment of liver function. Three types of jaundice were noted: The first characterized by an icteric tinge, with an increase of urobilin in the urine and a positive indirect, or at least a delayed direct, van den Bergh test; the second characterized by bile as well as urobilin in the urine, deeper jaundice and a biphasic van den Bergh reaction; the third type in which there evidently was a cholangitis with still deeper jaundice, large amounts of bile in the urine and an immediate direct van den Bergh reaction. Sodium thiosulphate intravenously did not influence these toxic effects. There was no increased fragility of the red cells demonstrable. In one case there was paralysis of the lower limbs, with loss of reflexes and absence of sensory changes. Psychopathies were rare. The lead preparation was given intravenously, and the dosage varied according to the case, usually being as follows: Two doses of 20 cc. and then two doses of 15 cc. of the 0.5 per cent preparation at ten-day intervals, when possible. The patient was then given a month's rest. Then smaller doses, amounting to 10 cc., were given at varying intervals, until a total of 120 cc., or 0.6 gm. of lead, was reached. In cases where the tumor was of slow growth smaller doses were administered from the beginning, and some of the more acute toxic effects avoided. At the end of the first five-year period 247 patients had been seen; 227 of these treated and 50 derived some benefit. In some of the cases not benefited changes occurred in the tumors, such as lobulation and edema, while some patients died as the result of the destructive action of the lead on the growth. Besides the treatment by lead, surgery and radiotherapy were also used wherever it was thought these would be of aid. The author gives the following figures on the 227 cases treated from November 9, 1920, to November 9, 1925: Died before treatment could be completed, 50; died of intercurrent affections, 3; died after treatment, including 2 deaths from acute nephritis, the result of lead poisoning, 106; died as a result of extensive destruction of growth by lead, 4; too recent for results to be estimated, 14; complete treatment refused, but patients are leading normal lives, 9; disease completely arrested, 10; believed cured and treatment stopped, 31; total, 227.

PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

Ketosis in Childhood.—COHEN (*Arch. Pediat.*, 1926, 43, 763) reports 8 cases, and states that there are three types of ketosis in childhood, which are classified according to their carbohydrate metabolism. The

first of these types is due to a depletion of carbohydrate reserves of the body by starvation and shows a hypoglycemia. This is quickly relieved by a relatively small amount of carbohydrate. The second type is one where the carbohydrate metabolism is abnormal. This form is always caused by infection and may be due either to a temporary pancreatic insufficiency or to a lowered hepatic function. The apparently diabetic type is best treated by glucose and insulin, and the apparently hepatic type can be relieved by glucose alone, except in severe cases where insulin seems to be indicated. The third type is one where the blood sugar is normal, the carbohydrate metabolism is normal, but glucosuria is present and the cause is an infection. This type can be cured by glucose alone. The suspected mechanism in this type is a deficient glycogenolysis or an excessive glyconeogenesis. This type is best treated with glucose alone in spite of the glucosuria. He reminds us that in all cases of ketosis fluids should be forced and bicarbonate should not be given but a buffer alkali may be used if an alkali is indicated.

The Prevention of Measles by Immune Goat Serum.—TUNNICLIFF and HOYNE (*J. Am. Med. Assn.*, 1926, 87, 2139) immunized goats with green-producing streptococci diplococci and their filtrates, and an anti-bacterial and antitoxic serum was produced. From 4 to 6 cc. of immune goat serum were given to children, aged one year or over, and to a few nurses, with a negative history of measles after definite exposure to measles. All persons who did not receive serum and all persons who received serum five days or more after exposure developed measles. Goat serum prevented measles in 45 per cent of persons who received serum on the fourth day after contact with measles patients, and in 97 per cent of those who received it within the first three days after exposure. All infants under one year of age who received serum after the fourth day of exposure developed measles. Of infants given serum within the first four days after exposure, 98 per cent failed to show any signs of the disease. Reactions to the goat serum were observed in 12 per cent of those injected. Although the duration of passive immunity with immune goat serum, as with human convalescent serum, is only a few weeks, the serum appears to be useful in preventing measles in very young and sick children and in stopping epidemics in institutions, where the inconvenience of an epidemic is great and the mortality may be high.

The End Result in the Treatment of Diabetes Mellitus in Children.—JOSLIN (*J. Am. Med. Assn.*, 1927, 88, 28) states that more than one-half of 395 diabetic children treated since 1898 are known to be alive. The duration of 8 cases, 3 of which died and 5 of which are living, has exceeded ten years. The author divides the period of his observation into the Naunyn Period, from 1898 to 1914; the Allen Period, from 1914 to 1922; the Banting Period, from 1922 to 1926. Of these period groups, at the time of his report, 1 child observed during the Naunyn Period was still alive. There were 52 living from the Allen Period and 147 from the Banting Period. The duration of the 51 fatal cases, which occurred during the Naunyn Period was two and one-tenth years. The duration of the 110 fatal cases during the Allen Period was

two and four-tenths years. The 34 fatal cases which occurred in the Banting group, up until the time of the report, had a duration of two and six-tenths years. The duration of the disease in 52 children now living, but who were first treated during the Allen Period, is six and six-tenths years. During this period the terms "acutely fatal diabetes" and "complete diabetes" were abolished. The author feels that the pathologic and clinical evidence justified the hope for the future of the diabetic child. The child with diabetes is the true diabetic patient, as he sets the standard for the rest and is the sentinel for the army of 1,000,000 diabetic patients in this country. The diabetic children deserve the best protection which modern preventive medicine can afford.

Congenital Icterus with Normally Developed Biliary Tract.—DE LANG (*Jahrb. f. Kinderh.*, 1926, 114, 15) presents the clinical data of congenital icterus in a baby who succumbed five days after birth. The blood study made before death revealed a slight neutrophilic leukocytosis. Vacuoles were observed in the cytoplasm of several polymorphonuclear leukocytes. Toxic granules were found in 80 per cent of the neutrophilic polymorphonuclear leukocytes. No evidence of sepsis nor syphilis was found at autopsy. The liver was not enlarged, but histologic examination showed a slight fatty degeneration of the liver parenchyma and a severe phagocytosis of erythrocytes and erythroblasts. There was a large increase in the iron content of the spleen. No abnormality in the anatomy of the biliary tract was seen, and it was concluded that icterus was caused by intrauterine intoxication.

Intraperitoneal Infusion.—TEZNER and EBEL (*Monatsschr. f. Kinderh.*, 1926, 33, 294) report the administration intraperitoneally of from 60 to 200 cc. of physiologic solution of sodium chlorid, normal salt solution, or 6 per cent dextrose, to 67 babies who were suffering from nutritional and parenteral disturbances and infection toxicoses. In most instances from 7 to 8 infusions were given to each infant, 1 injection being given only in twenty-four hours and in a few cases 2 in twenty-four hours. The total number of injections given was 171. In 4 of the 67 life was undoubtedly saved, 2 developed peritonitis and the total mortality was 51 per cent.

The Pathology of Diabetes in Children.—WARREN (*J. Am. Med. Assn.*, 1927, 88, 99) gives the case reports of 10 cases of diabetes in children, 9 of whom died in coma and 1 was accidentally killed. From a study of the the postmortem findings, he says that the pancreas in diabetic children may be small, but the amount of island tissue is not sufficiently reduced to account for the disturbed metabolism in most cases. Diabetes in children is a severe disease, but 1 of the cases included in this report ran a course of twenty-nine years, being under observation from the time the child was nine years until she died, at the age of thirty-eight years. Lymphocytic infiltration of the islands, as found in the children, is a lesion not met with in older diabetic patients, and hyalinization of the islands is not found in the young. There is little change either in the islands or in the acinous tissue, although these changes are frequently reported in the old, and those

changes that may be present do not appear sufficient to account for the marked disturbance in function. Considering the anatomic pathology of diabetes in children, one is led to the hope that through treatment which allows the elements of time to act, irreversible changes in the pancreas may be avoided.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Syphilitic Myocarditis in the Rabbit.—BROWN and PEARCE (*J. Exper. Med.*, 1926, 43, 501) encountered 6 cases of pronounced granulomatous myocarditis in the course of routine postmortem examinations of rabbits infected with *Spirochaeta pallida*. Spirochetes were not demonstrated in the lesions, but the clinical history and the gross and microscopic appearance of the lesions seemed to warrant a diagnosis of syphilitic myocarditis. The myocarditis developed at about the time other generalized manifestations of disease usually occur, and in several instances was closely associated with the development of such lesions; hence, the myocardial involvement in the rabbit is an early event rather than a later event in the evolution of the disease. The lesions measured 1 cm. or more in diameter, and were readily seen macroscopically as circumscribed, pale yellowish-gray masses of tissue, usually in the wall of the left ventricle and closely associated with the endocardium. The distinctive histopathologic features observed were a primary degeneration and necrosis of individual muscle fibers associated with a growth of myxomatous connective tissue and infiltration of wandering cells with a predilection for tissues in the immediate vicinity of small and medium-sized bloodvessels. These findings are similar to the description given by Warthin of syphilitic myocarditis in man. The only essential difference is the absence of a perivascular accumulation of wandering cells, but even this difference is offset by a perivascular arrangement of the lesions themselves. These are the first cases of syphilitic myocarditis or of visceral syphilis in the rabbit that have been reported.

Effect of Thyroidectomy and of Thymectomy in Experimental Syphilis of the Rabbit.—PEARCE and VAN ALLEN (*J. Exper. Med.*, 1925, 43, 297) were able to demonstrate in experimental rabbit syphilis that the integrity and balance of the glands of internal secretion play an

important rôle in the mechanism of defense of the host against this infection. Surgical removal of the whole or part of the thyroid gland or of the entire thymus gland, shortly before inoculation in the testicle with *Spirochaeta pallida* (Nichol's strain), is followed by well-defined differences in the clinical manifestations in the disease. In the case of complete thyroidectomy the effect was, in general, one of increased severity, as manifested especially by the shortened incubation period and pronounced grade of both the primary and metastatic orchitis, the much higher incidence of generalized lesions (especially cutaneous), and the distinct tendency for all lesions to be more enduring than in the control animals, or, it may be added, than is ordinarily the case in normal rabbits. Partial thyroidectomy (one lobe and the isthmus of the gland removed) resulted in a disease that was generally less severe than that of the controls, as shown by the milder character of the primary and metastatic orchitis, but especially by the low incidence of generalized manifestations and by the relatively short duration of all the lesions. These contrasting effects of complete and partial thyroidectomy occurred in a repeated experiment, but were more marked in the original. The authors are not able to speak so definitely about the effect induced by ablation of the thymus, since it was studied in but one experiment. The disease which developed after complete thymectomy was of a mild type, much less severe than in the group of completely thyroidectomized animals and, on the whole, somewhat less so than that of the controls. This was particularly evident in the metastatic lesions of the genitalia and the number, incidence and distribution of generalized manifestations. In many respects the general plane or grade of infection was similar to that of the group of partially thyroidectomized rabbits.

Variations of Cutaneous Toleration for Roentgen Rays.—MACKEE and ELLER (*J. Am. Med. Assn.*, 1926, 87, 1533) tested 210 patients for Roentgen ray toleration before instituting routine therapeutic treatment for acne vulgaris. These tests were performed as a prophylactic measure after observing that an occasional person, especially an adolescent blonde, will exhibit an erythema following the administration of $\frac{1}{4}$ skin unit of unfiltered Roentgen rays. Because of the possibility of telangiectasia occurring even after an exceedingly mild and evanescent erythema, it is of extreme importance to avoid any visible reaction. Telangiectasia is cosmetically objectionable; it may be accompanied or followed by other sequelæ, such as atrophy, pigmentation, depigmentation, scleroderma, keratoses, ulceration and even epithelioma. All patients were tested with $\frac{1}{4}$, $\frac{1}{2}$ and $\frac{3}{4}$ unit doses, unfiltered. The areas used were about the size of a postage stamp, and they were situated either on the inner surface of the thigh or on the flexor surface of the forearm. The unit of measurement corresponds with the so-called standard erythema dose; that is, the amount that will usually effect a definite erythema on the flexor surface of the forearm of young adults, and that will cause defluvium of scalp hair in children. Of the 210 patients, 11 (5 per cent) developed erythema with $\frac{1}{4}$ unit, 31 (15 per cent) with $\frac{1}{2}$ unit and 54 (25 per cent) with $\frac{3}{4}$ unit. As was to be expected, patients with light hair and fair skin show a higher percentage of reactions to small doses than do those with dark hair. Including

both sexes, there were 162 patients with dark complexions and 48 with light complexions. Of the latter, 4 (8 per cent) showed erythema with $\frac{1}{4}$ unit, as compared with 7 (4 per cent) of the former. When erythema occurred it developed in about five or seven days, and endured from one to several weeks. . . . Ninety-seven of the 210 patients (46 per cent) exhibited pigmentation as a result of $\frac{1}{4}$ unit, 106 (50 per cent) with $\frac{1}{2}$ unit and 109 (51 per cent) with $\frac{3}{4}$ unit. Approximately 56 per cent of those with dark skin developed marked pigmentation, while about 39 per cent of those with light skin developed pigmentation. It appeared about one week after treatment, disappearing usually in eight weeks. Pigmentation alone is not considered to be injurious. The results were about the same with filtered and unfiltered radiation. Because of these observations, supporting the well-known fact of considerable variation of susceptibility to Roentgen rays, the authors believe that the testing of a patient's skin for toleration before instituting a course of treatment may possibly add an additional safety factor to the techniques.

OBSTETRICS

UNDER THE CHARGE OF

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Placenta Previa: A Study of 165 Cases.—BRODHEAD and LANGROCK (*Surg., Gynec. and Obst.*, 1927, 1, 39) review a study of the treatment of 165 cases at the Harlem Hospital. Of the 165 cases, 100 were marginal, 39 central, 20 lateral and 6 unknown. Version was done in 106 cases, normal delivery in 28, breech extraction in 17, Cesarean section in 9, forceps in 4 and craniotomy in 1. They agree that central placenta previa in a primipara with an undilated cervix, section is advisable; but in multiparæ section is debatable. They believe all these cases should have the uterus and vagina tightly packed with iodoform gauze. Blood transfusion is of the very greatest benefit. In this series there were 18 deaths, 3 of the women being admitted moribund and 1 losing her life from tuberculosis; 110 babies were lost.

Maternal Mortality in an Outdoor Clinic?—BAILEY (*Am. J. Obst. and Gynec.*, 1926, 12, 817) reviews 4488 cases delivered in the outdoor service of the Cornell Medical School. There was a total of 12 obstetrical deaths—1 in 374 cases, or 2.67 per 1000 births. These statistics are lower than New York State statistics, and the author believes these

low figures are due to the transfer of the major operation cases to suitable hospitals as early in the labor as the complications became evident and to the aseptic technique in the conduct of labor.

Gastric Juice during Pregnancy.—ARZT (*Am. J. Obst. and Gynec.*, 1926, 12, 879), of St. Louis, after studying a series of cases by fractional gastric analysis, concludes that the free HCl and total acid of the stomach contents are lower in pregnancy than in the nonpregnant and that dilute HCl acid is indicated in preventing early nausea and vomiting of pregnancy. This deficiency, he thinks, is not due to an actual deficiency of secretion, but to the neutralization of the acid by alkaline salts regurgitated from the duodenum into the stomach.

Ectopic Pregnancy.—CULBERTSON (*Illinois Med. J.*, 1926, 1, 487), in a recent paper based upon the study of 150 cases, state that 40 patients had no preceding amenorrhea. That is so common that now amenorrhea is disregarded as an essential in the diagnosis of ectopic pregnancy. The question of external hemorrhage associated with the well-known decidual cast described in the textbooks is practically never seen. In the differential diagnosis the essayist has come to regard it in this way. If the patient has a mass in the pelvis he thinks of ectopic pregnancy; if she has a mass in the pelvis with moderate amenorrhea he makes a diagnosis of pelvic hematocele.

The Diagnosis and Treatment of Pyelitis.—EISENDRATH (*Illinois Med. J.*, 1926, 50, 493) advises the following treatment: (a) Give large quantities of fluid by mouth if possible, if not, by proctoclysis, hypodermoclysis or through use of the duodenal tube; (b) absolute rest; (c) administration of alkalies and acids alternately; (d) urinary antiseptics; (e) use of one or more inlaying ureteral catheters; (f) lavage of the renal pelvis. He also advises the following: Never wait too long for operative intervention if the fever and other symptoms persist or increase in spite of medicinal treatment, and the use of the inlaying catheter or of pelvic lavage.

The Safeties of Ethylene Anesthesia.—GUTHRIE (*Surg., Gynec. and Obst.*, 1926, 43, 703) writes that since 1923 Drs. Luckhardt and Carter have given the medical profession a new anesthetic, ethylene gas, after much experimental work. The reason for developing a new anesthesia is that all of the previous materials used had some serious objection to them, either they were objectionable to the patient or more or less dangerous in certain cases, complicated with pulmonary and gastrointestinal complications. It was first used by Dean Lewis and W. E. Brown, who believed it safe and a satisfactory anesthetic. It is known to be a highly explosive gas and several instances occurred in which explosions took place from the static friction spark. The recent appliances for giving this gas have done away somewhat with the possibility of ignition and explosion. The authors warn against the use of the cautery. The odor is sweet and often disagreeable. The advantages are enumerated, that it is easy to give and take, the rapidity of induction, the rapid return of consciousness and the absence of postoperative vomiting. Relaxation is easily obtained for the reduction of fractures

and dislocations of the larger joints. The gas does not stimulate the respiratory center. The skin is closed; the patient's color is good if the anesthetic is properly given. Oxygen may be given and is a good rule, equivalent to 20 per cent, the average percentage of oxygen in the air. The secretions are not excessive; the excitability usually seen in other anesthetics is usually absent. Ethylene is particularly recommended in poor surgical risks, such as cardiovascular, pulmonary or diabetic complications. In thyroid surgery it is especially recommended. Those general surgeons who have boldly made use of this anesthetic in their work report favorably a great reduction in post-operative pulmonary and gastrointestinal complications, and in their general operative mortality.

GYNECOLOGY

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Total versus Subtotal Hysterectomy for Fibroids.—The perennial operative question relative to the value or rather advisability of the total hysterectomy in the treatment of fibroids has been again brought forth by GRAVES (*Am. J. Obst. and Gynec.*, 1926, 12, 217), who takes the negative side of the question. He states that the mortality percentage in supravaginal hysterectomies for fibroids is low and he feels certain that if he performed total hysterectomy as a routine, the number of deaths would have considerably exceeded the incidence of cancer in the cervical stump. The mortality percentage in supravaginal hysterectomy for all causes, though much higher than that for fibroids, is nevertheless satisfactorily low, considering the desperate character of many of the cases and in the more difficult cases total hysterectomy would often have subjected the patient to a risk greater than that of a later cancer of the stump. If total hysterectomy is to be employed as a routine for fibroids consistency demands that it be used in all cases requiring hysterectomy, especially in pelvic inflammatory disease. He points out that a patient who dies from an operation is irrevocably dead, while one who survives the operation but later develops a cancer of the stump has a definite though small chance of being cured of cancer. However, when the condition of the cervix is in doubt total hysterectomy is the operation of choice. Polak has been one of the most ardent champions of the total operation, and it is of interest to note that in discussing the above paper of the author he stated that he has modified his view of this subject. Although there is very little difference in

mortality in the two operations in his hands, the supravaginal operation gives a smoother convalescence. He now does the complete operation only in those cases where there is extensive disease of the cervix as a complicating factor. He is forced to conclude, however, that his results are better since becoming more conservative.

Value of Blood Sedimentation Test.—On several previous occasions we have presented articles relating to the blood sedimentation test as a diagnostic and prognostic aid in pelvic inflammatory disease. At the meeting of the American Gynecological Society in May, 1926, the subject was thoroughly considered and on the whole received quite favorable comment. BAER and REIS (*Am. J. Obst. and Gynec.*, 1926, 12, 740), who were among the first in this country to use the test in gynecology, come to the conclusion that the test is more useful than the temperature curve or the leukocyte count in determining the presence or absence of infection. They believe that a sedimentation time of more than two hours rules out infection in the existing pelvic pathology. The test is a further aid in determining the safe time for operation, sixty minutes being the lower limit of safety. As a prognostic index, they believe that the test is more delicate than either the leukocyte count or temperature curve. In recording their experiences with this test at the same meeting, POLAK and MAZZOLA (*Am. J. Obst. and Gynec.*, 1926, 12, 700) state that it is well established that foci of infection may remain quiescent for weeks, months or years, only to undergo exacerbation after operation, when they may produce peritonitis, parametritis and blood stream infections. Apparently the bacteria are buried in the tissues and are surrounded by a limiting wall of connective tissue. Trauma produces dissemination. Heretofore, the clinical history and Simpson's rule have been the only guides as to the safe time for operation, but the sedimentation test adds another safeguard. For example, in incomplete septic or potentially septic abortions appreciation of a rapid sedimentation time when associated with a normal temperature curve and a low leukocyte count, has saved a number of women from having their uteri curetted and Nature's barriers broken down. They believe that its routine employment as a preoperative procedure in gynecologic cases will likewise safeguard the woman who is potentially infected or warn us of her infectivity when the local barriers are broken down.

Effect of Oöphorectomy on Metabolism.—According to GEIST and GOLDBERGER (*Am. J. Obst. and Gynec.*, 1926, 12, 206), there is very little known at the present time concerning the physiology of the ovary except in its relation to the generative function, and comparatively few studies have been undertaken to determine the effect on the general metabolism after bilateral oöphorectomy. Most of these investigations have been carried out on animals. They have attempted to study the effects of castration on the basal metabolism, weight and blood chemistry, in order to determine if in human females living under normal conditions the removal of the gonads exerts any definable effect, also to ascertain, if possible, whether the removal of the ovaries is followed by results of sufficient physiologic importance to make it advisable to conserve them when technically possible. Summing up the results of

their investigations, it would seem that castration in women with previously functioning ovaries does not result in a consistent variation of the basal metabolism or the body weight. There seems to be no definite relationship between the variations in weight and basal metabolism. Likewise the blood chemistry and pressure remain uninfluenced. These results may be due to: (a) The inaccuracy of our present clinical methods of examination; (b) the influence of other important extraneous factors; (c) the absence of any ovarian influence. The changes above mentioned are not of sufficient fundamental importance to warrant their being used as an argument for the conservation of the ovaries.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Concerning Radical Operation on the Internal Ear—in Diseases Secondary to Otitis Media.—From an experience with 117 cases, LUND (*Ugeskr. f. Læger.*, 1926, 88, 654) advises that a lumbar puncture be performed in every case of acute destructive labyrinthitis. In the event that two cells per cubic millimeter are found in the spinal fluid, and there are no symptoms of meningeal irritation, he believes that the lumbar puncture should be repeated in twenty-four hours. If there are more cells than two or if other symptoms are noted he thinks a radical operation should be done immediately.

Experiments with Tonsils.—Upon inoculating rabbits with fresh extracts of human tonsils and adenoids, RUSS and SUCHANEK (*Wien. klin. Wchnschr.*, 1926, 39, 883) found that a relatively small dose was fatal. Sublethal doses produced a leukopenia and thrombopenia which lasted for several hours, whereas extracts from lymph nodes and various viscera caused a leukocytosis. The only exception occurred when placental extracts were employed. In these instances the reactions simulated, to a degree, those seen from tonsillar extracts.

Displacement Irrigation of Nasal Sinuses: A New Procedure in Diagnosis and Conservative Treatment.—As the irrigation of sphenoid and posterior ethmoid sinuses has been difficult by virtue of their positions and the inaccessibility of their ostia, PROETZ (*Arch. Otolaryngol.* 1926, 4, 1) describes a simple method of introducing fluids into these sinuses without traumatizing them. The patient is placed in the supine position, with the head projecting beyond the top of a table or chair and extended until the tip of the chin and the external auditory meati lie in the same vertical plane. The fluid to be introduced is allowed to flow through the nostrils from a syringe into the "V"-shaped pocket

between the junction of the face of the sphenoid with the cribriform plate of the ethmoid. By applying gentle suction (not more than 3 pounds) intermittently to one nostril, the other being closed and the palate and tongue being held in the "K" position to seal the pharynx, the air is withdrawn from the sinuses and the fluid replaces it. After about twelve alterations of the suction the sinuses usually are filled and the patient is returned to the erect position, the fluid remaining *in situ* for an indefinite period. The procedure can be employed as a diagnostic or therapeutic agent by the use of proper solutions. The author says that his method "is not a substitute for surgical measures in those cases in which extensive permanent tissue changes have taken place, but may prevent such changes if instituted before they have occurred."

Clinical Observations on the Use of the Audiometer in Testing the Hearing.—It is well known that there are several methods of testing the hearing, such as tuning forks, watch, spoken voice and whisper. Recently an electrical instrument of precision has been devised to aid in giving more exact information relative to audition. Realizing the worth of this contrivance—the audiometer—NEMZEK and HAYS (*Laryngoscope*, 1926, 36, 565) regard as its greatest advantage the absolute quantitative analysis it affords, not only in noting whether treatment is beneficial or detrimental, but also in ascertaining if a gain in hearing is psychologic or real. After presenting and discussing the audiograms of representative types of deafness, the authors conclude from their investigations that the audiometer gives a rapid and accurate method for testing the hearing; that it shows in what part of the hearing apparatus the pathologic lesion is present; that it indicates when conductive and perceptive lesions are combined; that its greatest value lies in its ability to definitely tell whether an individual under treatment is receiving any benefit; that it permits of comparisons of hearing tests by different individuals. They feel, however, that the audiometer has one drawback—in children up to six or seven years it is not accurate and is more tedious in testing the hearing than other methods, because it serves as a toy and it is impossible to have them signal when the tones are no longer heard. It is a great help, on the other hand, in testing the hearing of children who are so-called deaf mutes.

Phenobarbital in the Prophylaxis and Treatment of Acute Cocain Intoxications.—Since cocain is now used so generally in rhinologic practice, many untoward reactions to this drug frequently occur, especially in those who exhibit an idiosyncrasy to it. This is particularly the case when the cocain is applied in the "flake" or powdered form, the resultant intoxication manifesting itself by loquacity, restlessness, tremor and palpitation, which may merge rapidly into a profound depression associated with cold clammy sweats, pallor, syncope and even death—the result of overstimulation of the cerebral cortex. Recently TATUM, ATKINSON and COLLINS (*J. Pharm. and Exper. Therap.*, 1925, 26, 325) have shown by animal experimentation that sodium barbital and paraldehyd increased the minimal lethal dose of cocain and also raised the tolerance when administered hypodermically. Employing these facts clinically, GUTTMAN (*Arch. Otolaryngol.*, 1926,

4, 304) has given 3 gr. phenobarbital by mouth to patients thirty minutes before the topical application of cocain. From his observations, although he states that the number of cases is small, the author believes that phenobarbital is a very valuable drug in the treatment of acute cocain poisoning and as a prophylactic in sensitive persons. He also says that its intravenous use, as suggested by other workers, in cases of severe intoxications or collapse due to cocain is indicated on a rational basis. More recently LESHURE (*J. Am. Med. Assn.*, 1927, 88, 168) reported the use of diethylbarbituric acid (barbital) or its sodium salt (sodium barbital) before local anesthesia with cocain in 100 patients without any symptoms of cocain toxicosis. Sodium barbital is given by mouth in 6- to 12-gr. doses at least a half hour before applying the cocain. The author says that "clinically, barbital alone appears to be as efficacious as when combined with paraldehyd, although for intravenous use the latter drug would be of considerable value."

RADIOLOGY

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Nontuberculous Peribronchitis Simulating Occult Tuberculosis.—MEADER (*J. Am. Med. Assn.*, 1926, 87, 139) describes a mild, subacute, nontuberculous peribronchitis which may produce interference with the patient's comfort and economic efficiency wholly out of proportion to the physical signs detectable on casual examination. The process primarily involves the peribronchial lymphatic system and the tracheo-bronchial and hilum lymph nodes with secondary involvement of the parenchyma. In the differentiation from occult tuberculosis lesions predominantly or wholly of the apexes have been regarded as probably tuberculous and of the lower lobes as probably nontuberculous. The appearance of different age in different lesions, as emphasized by Dunham, while presumptive evidence of tuberculosis may be seen in nontuberculous lesions. Calcification of lesions favors the diagnosis of tuberculosis. These, when evaluated in the light of the whole clinical picture, represent safe roentgenologic criteria. Properly treated, these conditions are susceptible of marked relief; untreated, they tend to the development of more marked and serious involvement.

The Retention of Vegetable Material in the Stomach.—BRYAN (*J. Am. Med. Assn.*, 1926, 87, 397) states the retention of vegetable material in the stomach, except in cases of complete obstruction of the pylorus, is rare. The cases reported have all been compact masses of

vegetable matter and removed as such. Six were composed largely of persimmon, 1 entirely of pumpkin, and the others of various vegetable fibers. Two cases were complicated by gastric ulcers. In the other cases no organic lesions were demonstrable. In the case presented the retained matter was composed of celery fibers, prune and raisin skins and other cellulose material which could not be identified. The mass was soft and loose and had to be removed with a spoon and by sponges on a sponge stick. The man, aged fifty-five years, a native of India, three years before began to have abdominal distress, first after meals and later constantly. There was occasional vomiting. At the same time there was a dull pain in the epigastrium and across the abdomen. He had intermittent attacks of diarrhea. Roentgenoscopic examination revealed an irregular network structure of alternating areas of opacities and nonopacities which could be changed by palpation. There was a six-hour and twenty-four-hour retention. A gastrotomy demonstrated retained foreign material. The patient had an associated diabetes.

Roentgenologic Diagnosis of the Anatomopathologic Varieties of Pulmonary Tuberculosis.—MEIER (*Fortschr. a. d. Geburtsh. u. d. Roentgenstrahlen*, 1926, 34, 456) holds that it is possible with the Roentgen ray to determine with accuracy the anatomopathologic character of tuberculosis in about 75 per cent of the cases; that distinction between predominantly productive, indurative or exudative varieties is feasible; that, although many cases are of the mixed forms, these also can be recognized roentgenologically. In the Roentgen picture the productive (nodular proliferative) nodule-forming variety appears as irregularly shaped shadows, some of which are elongated, others rounded, often bordered in rosette fashion and discrete, but more or less grouped. The center of a single area shows its induration or caseation by an increased density, so that each focus has a light areola. These areas are easily distinguishable, as a rule, from hematogenous miliary tubercles, which are usually all round but of varying sizes. The areas of exudative-lobular-lobar tuberculosis produce larger shadows. These also are irregularly bordered, have a spot of increased density (caseation) and a gradual peripheral clearing which often overlaps a neighboring focus. Thus the picture of the exudative form has an indefinite washy appearance. The exudative foci are distinguishable from the productive by their size, although exudate may be imitated by the hyperemia about a productive focus. The indurative or cirrhotic form is characterized by: (1) Healing processes in productive or exudative areas; (2) atelectasis and collapse of surrounding lung tissues; (3) vicarious emphysema in the vicinity of indurated and atelectatic sections of the lung. Thus the picture of the indurative form has an extraordinarily variegated aspect with small and large diffusely bordered shadows surrounding denser areas. These latter correspond usually to hyalinized scar tissue and fibrous streaks. The fleck-like shadows in the vicinity of the indurated areas are due to atelectasis and collapse of adjacent lung tissue. Vicarious emphysema produces clear spots. Heart and large vessels are often displaced by scar contraction. All three forms may be complicated by cavities. The cavity of the productive form has smooth walls which are sharply

delineated. The cavity of the exudative form is irregularly shaped with clear areas and marked densities. The cavity of the indurative, cirrhotic form is clear, irregular in shape, and has fibrous strands in its vicinity.

PATHOLOGY AND BACTERIOLOGY.

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The Vascular Mechanism of the Spleen.—In his recent work on the spleen, ROBINSON (*Am. J. Path.*, 1926, 2, 341) has brought much to light concerning the minute structure of the spleen, the distribution of its arteries, their relation to the pulp and the bloodflow through the spleen. Following death or extirpation, the spleen immediately contracts. The spleen, a highly vascular organism whose chief function appears to do with blood purification and conversion of hemoglobin, is a lobular structure divided by trabeculae, consisting of muscle, elastic and connective tissue. The interlobar veins are closely associated with the trabeculae, while the arteries occupy a more central portion of the lobule. The pulp in stereoscopic view consists of a delicate network of starlike cells having long, irregular, protoplasmic processes running in all directions, uniting one cell with another, forming a spongy structure with pulp spaces. The same cells form a covering for the trabeculae and larger bloodvessels. These cells are phagocytic for colloids and belong to the reticuloendothelial system. It was demonstrated that the capsule and trabeculae, besides acting as a supporting framework, in a large measure control the flow of blood through the pulp spaces by their contraction and relaxation. The arteries are short and stouter than the veins, and after penetrating the Malpighian corpuscles appear to end abruptly in globoid masses of cells—the ellipsoids. The ellipsoids are pear shaped and are distributed uniformly throughout the pulp. The arterioles enter at the blunt end and the exit is at the small end. The cells making up the ellipsoid are closely packed about the capillary which remains quite patent. These cells are of the same type as the pulp cells. The intercellular spaces communicate freely with the adjacent pulp spaces. The terminations of the arterioles appear to blend with the walls of the pulp, but in most cases the end capillary terminates in an ampullary dilatation with openings into the surrounding pulp spaces and making the ampulla really an exaggerated pulp space. Coursing through the pulp are the large venous sinuses closely associated with the trabeculae.

The finer venous branches form a free network of anastomosing channels intimately associated with pulp and ellipsoids. Their walls are incomplete, being made up of parallel rows of elongated endothelial cell loosely bound together by protoplasmic processes of the neighboring pulp cells, and leaving open slitlike spaces in their walls. Hence we have in the spleen an open circulation, the blood passing from the arterioles to the ampullæ or exaggerated pulp space into pulp spaces proper and from here into venous channels.

Epidemiology of Scarlatinal Throat Infection Sine Exanthemata.—

The occurrence of pharyngitis in persons with *Streptococcus scarlatinæ* in their throats but who develop no skin rash has been previously reported by STEVENS and DOCHEZ. Certain problems arising from these findings have been further studied by the same authors (*J. Am. Med. Assn.*, 1926, 87, 2137), using family group cases of infection to obviate difficulties in epidemiology. Three such case groups were carefully followed in which there occurred scarlet fever in one member of the group and acute angina, pharyngitis or sore throat among other members. The identity of the streptococci isolated from the cases in each group was determined by agglutination and agglutinin absorption. Complete absorption did not occur with the serums and strains of different groups. Two cases of scarlatinal angina occurred in persons with faintly positive Dick tests, although, as a rule, those not showing a rash are those with negative skin reactions. One patient with a previous history of scarlet fever developed a throat infection with *Streptococcus scarlatinæ*. It was also clearly shown that the same strain of *Streptococcus scarlatinæ* may cause clinical scarlet fever or scarlatina sine exanthemata and that the antitoxin is an efficient therapeutic remedy for both.

Streptococci from the Feces—Enterococcus.—Since the time of Escherich (1886), but particularly after the work of Thiercelin (1899), the streptococci of the intestinal tract have been interesting and confusing. Until recent years the term enterococcus (Thiercelin) has been found almost exclusively in the French literature (enterocoque). The work of SCHONFELD (*Centralbl. f. Bakteriol.*, 1926, 99, 388), MEYER and SCHONFELD (*Centralbl. f. Bakteriol.*, 1926, 99, 402) and MEYER (*Centralbl. f. Bakteriol.*, 1926, 99, 416) was undertaken in the attempt to find more precise points differentiating the enterococcus from other streptococci, particularly the *Streptococcus viridans* (Schottmüller). The characters given for the diagnosis of enterococcus are: (1) Resistance to 20 per cent bile; (2) fermentation of the glucoside esculin. The characters almost always found are: (a) Heat resistance (60° C. for fifteen minutes or more); (b) fermentation of mannit; (c) diffuse growth in bouillon; (d) oval or lancet forms of diplococci. The *Streptococcus viridans* (practically all from the oral cavity) is sensitive to heat, usually also to bile, fails as a rule to ferment esculin and mannit, generally gives a granular growth in bouillon and shows round cocci in the chains. The enterococcus, as a rule, grows on blood agar as gray-white colonies, with a variable amount of green color in the medium. However, Meyer (p. 416) reported nine strains of hemolytic enterococci from about 300 carefully studied strains of enterococci. The Strep-

tococcus viridans almost always grows as green colonies with greening of the medium. The attempts to differentiate enterococcus from the milk streptococci (*Streptococcus lactis*) did not give such clean-cut group characters, and the conclusion is drawn that these streptococci do not belong to a uniform group. They strongly opposed calling the enterococcus a lactic-acid streptococcus. Meyer considers the enterococcus an important cause of infections about the gall bladder, appendix, kidney and about the bowel. It is to be recalled that the *Streptococcus faecalis* of English and American literature probably belongs to the enterococcus group, but that "enterococcus" includes other streptococci which have not been grouped under *Streptococcus faecalis*. GUNDEL (*Centralbl. f. Bakteriologie*, 1926, 99, 469) discussed the etiologic importance of "enterococci" in bladder and kidney disease and the relation of "enterococci" to the lactic-acid streptococci. He did not believe it possible to separate the "enterococci" from the lactic-acid streptococci of the oral cavity, intestinal and urinary tracts. He did not, however, use the same criteria as Meyer and Schonfeld did for differentiation. He nevertheless recommended using the term enterococcus for these cocci found in diseased conditions, because it is established in international literature.

HYGIENE AND PUBLIC HEALTH

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The Relative Incidence of Typhoid Fever in Towns, Cities and Country Districts of a Southern State.—LEACH and MAXCY (*Pub. Health Repts.*, 1926, 41, 705) report that the lowest incidence of typhoid in Alabama is in the country, the next lowest in the larger cities and the highest in small towns. One hundred and sixteen towns, varying in population from 500 to 2500, constituting 7 per cent of the total population, furnished 28 per cent of all cases of typhoid fever. The facts point to the localities in which improvement can be expected and where effort must be expended.

A Further Study of Butter, Fresh Beef and Yeast as Pellagra Preventives, with Consideration of the Relation of Factor P-P of Pellagra (and Black Tongue of Dogs) to Vitamin B.—GOLDBERGER, WHEELER and ROGERS (*Pub. Health Repts.*, 1926, 41, 297) present the following

summary and conclusions: (1) Previous trials of butter in a daily quantity of about 140 gm. (5 oz.), using a Georgia product, had practically invariably failed to prevent recurrence of pellagra. Further trials with a Vermont product proved no more favorable than those with the Georgia butter; butter would seem to be poor, or lacking, in the pellagra-preventive factor or factors. (2) The pellagra-preventive action of a daily allowance of 200 gm. (7 oz.) of fresh meat in the form of lean beef was tested and found capable of completely preventing the disease, thus proving that fresh beef contains the pellagra-preventive factor or factors; the beef-supplemented diet, though adequate for pellagra prevention, was, during about half of the period of study, slightly deficient in the beriberi vitamin. (3) The pellagra-preventive action of a dried yeast extract was tested in a daily quantity of 15 gm. ($\frac{1}{2}$ oz.), and found efficient in preventing the disease; the yeast-extract-supplemented diet was adequate to prevent pellagra, but, during a part of the period of observation, was slightly deficient in the beriberi vitamin. (4) The results of the studies presented are believed to strengthen the interpretation of those previously reported, namely, that in the prevention and presumably causation of pellagra there is concerned a heretofore unrecognized or not fully appreciated dietary essential (factor $P-P$), and to indicate the probability that this may play the sole essential role in relation to the disease. (5) A statement of a preliminary character is made of some of the results of an experimental study of black tongue, and it is briefly pointed out that the substances that have been found to possess black-tongue-preventive potency have, when tried in pellagra, been found efficient preventives of the human disease and that those that had failed in pellagra, or were of low pellagra-preventive potency, when tried in black tongue have failed, or were feeble, as preventives of the canine disease. The working hypothesis has, therefore, been adopted that black tongue of dogs is the analogue of pellagra in man, and thus that factor $P-P$ is concerned in the prevention and causation of both black tongue and pellagra. (6) The relation of the factor $P-P$ to "water-soluble B" is considered and evidence is cited showing: (a) That the antineuritic factor (vitamin B *sensu stricto*) is distinct from the factor $P-P$ and does not in itself suffice for the growth of the rat; (b) that if the term "water-soluble B" includes, as some investigators have suggested, in addition to the antineuritic factor a so-called growth-promoting essential (possibly identical with Wildier's bios), this, like the antineuritic factor, is either inactivated by autoclaving, or does not suffice by itself for the growth of the rat; (c) that factor $P-P$ or some associated, and, in yeast, like $P-P$, thermostable factor (possibly the so-called growth-promoting factor) distinct from the antineuritic vitamin, though not sufficing in itself for the growth of the rat, is, in combination with the antineuritic, essential for growth in rats. (7) Whether factor $P-P$ is, as at present seems most probable, identical with the so-called growth-promoting essential heretofore included (with the antineuritic) in the term "water-soluble vitamin B," or whether these are distinct, further investigation must determine.

The Leprosy Problem in the United States.—DENNEY (*Pub. Health Repts.*, 1926, 41, 923) notes that leprosy has existed in the United

States for many years. The Gulf States constitute the most important focus as the disease spreads readily there. The number of lepers in the country is said to be, conservatively stated, as about 1200. The difficulty of securing accurate data is pointed out. The difficulty in establishing a national home for lepers, and even a state home, is considered. The national institution at Carville, La., is described, and the procedures with respect to admission and discharge are briefly discussed.

On the Control of Heart Disease in Childhood.—LOWENFELD (*Brit. Med. J.*, 1926, p. 817) states that the problem of cardiac disease in the young is one of the most serious issues presented to practical medicine today. According to one estimate, the onset of two-thirds of adult cardiac morbidity occurs during the period from five to fifteen years of age. Carditis in childhood is for all purposes a rheumatic manifestation, and in practice the control of heart disease in childhood means the control of the rheumatic child. Rheumatism is an exceedingly long-drawn out chronic infection which in all its forms should be considered as passing through three stages, the acute, the convalescent and the quiescent. The incidence of carditis can be diminished apparently by efficient handling of rheumatism in the acute stage. Only 24 per cent of those treated in hospitals for the first attack of acute rheumatism subsequently developed carditis, but heart disease developed in 88 per cent of those who were treated at home. By the establishment of clinics, the incidence of carditis can be reduced to a minimum. Clinics would serve as an instrument of research for increasing knowledge of the heart of the child and its response to rheumatic toxin. Records could be correlated and valuable light could be thrown on the nature of the disease.

The Administrative Control of Measles.—GODFREY (*Am. J. Pub. Health*, 1926, 16, 571) suggests a method of control based upon the fact that approximately 70 per cent of all measles cases occur in children under three years of age, whereas the population at this age amounts to but 6 per cent of the total. Present methods of attempting to prevent all cases of measles could be abandoned and all efforts be concentrated to prevent as many cases as possible in children under three years. A study of New York State (1915-1924) shows 595,234 cases of measles and 8036 deaths. In places of 50,000 to 200,000 population 18 per cent of the cases and 83 per cent of the deaths occurred in children under three years of age, as compared with 11 per cent of the cases and 61 per cent of the deaths in villages of less than 2500 people. In places of less than 200,000 population 35,930 cases were reported among children under three years. Of these, 1441 died—a fatality rate of 4 per cent. The disease is very apt to prove fatal to children under three years of age, therefore it is desirable to prevent the disease in children of this age group. This can be accomplished by intensive education of the parents of small children. Measles epidemics can be predicted with a fair degree of certainty by studying past records of the community and noting the usual interval between outbreaks. Nearly 90 per cent of the children under three years of age could be traced by referring to birth certificates. At the approach

of an epidemic the parents of these children could be warned of the danger of this disease. Health officers could instruct parents in the initial symptoms, and the need of reporting all cases and the necessity of good care, maintain a supply of convalescent serum or provide a physician to administer parental blood when needed. Each case would need the personal supervision of the public-health nurse to discover contacts and early cases. These should be passively immunized with either serum or parental blood.

This proposed method might be more laborious than those now in use, but it would provide a means of preventing deaths by keeping at the lowest possible minimum, the number of cases in children under three years of age and in older children in delicate health and by seeing that no child suffers from ignorant neglect.

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Penetration of HCN through Living Membranes.—F. J. BRINLEY (from the Laboratory of Zoölogy, University of Pennsylvania). Recent work by Osterhout shows that H_2S and CO_2 enter cells as undissociated molecules, and not as ions. As HCN is also a weak acid, it was thought advisable to study the effect of pH upon the passage of HCN through living membranes. The membrane used was frog skin. An artificial cell, constructed by stretching the skin over the open end of a hard glass tube was used. The inside of the cell was filled with a borax buffer, and the cell was then placed in a solution of HCN in a borax buffer. The cell was tightly stoppered and placed in a water bath for one hour, at which time equilibrium was reached. Samples from the inside and outside of the cell were titrated with fiftieth-normal $AgNO_3$. Experiments using different internal and external pH values were conducted. Results indicate that more HCN enters the cell when external pH was acid than when alkaline and that the penetration curve approximates that of the dissociation curve. HCN seems to enter largely as undissociated molecules rather than as ions. Varying internal pH did not affect the penetration of HCN.

Further experiments show that temperature and concentration affect the rate of entrance as well as the total amount of cyanid within the cell at equilibrium.

Microinjection Studies of Capillary Permeability: The Passage of Dyes in Relation to Capillary Pressure and Dilatation.—E. M. LANDIS (from the Department of Physiology, Medical School, University of Pennsylvania). In the study of capillary permeability it has been frequently found that a dye intravenously injected passes more rapidly

into tissue areas in which an active hyperemia has been induced. In view of the rise of capillary pressure found on direct measurement to occur in the hyperemia produced by heat and by urethane (*Am. J. Physiol.*, 1926, 75, 548), it seemed possible that pressure changes might be an important factor in determining the rapidity of filtration of a dye solution through the capillary endothelium. The experiments described were undertaken in order to find whether the passage of certain dyes was related primarily to capillary pressure as would be expected from the Starling hypothesis (*J. Physiol.*, 1896, 19, 312) or to the degree of capillary dilatation as suggested by Krogh (*Anatomy and Physiology of the Capillaries*, Yale University Press, 1922).

By the use of the microinjection technique previously described in detail, a series of perfusions of single capillaries was performed, using the vessels of the frog's mesentery. A fine micropipette, having a diameter at the tip between 4 to 8 μ , and filled with dye solution, was introduced into the lumen of a capillary. The pressure on the dye in the pipette was raised until it balanced the capillary pressure, which was recorded. A slow flow of the dye solution was maintained by raising the pressure in the micropipette 2 to 3 cm. above the observed capillary pressure. The time for a barely visible amount of dye to appear outside the capillary wall was taken, followed by a second pressure determination and the measurement of the diameter of the perfused vessel.

Using an 0.015 molar solution of toluidin blue in Ringer's fluid, 116 capillaries with diameters between 11 and 37 μ were thus perfused at pressure ranging from 5 to 30 cm. water. The results were grouped according to: (1) The diameter of the perfused vessel; (2) the pressure at which the perfusion was carried out. With increase of capillary diameter, the average time for visible passage of the dye remained practically the same, ranging between one and eight-tenths to two and three-tenths minutes. From these observations it seems that there is no measurable increase in permeability occurring with dilatation of the capillary. The same experiments grouped according to the level of capillary pressure at which the perfusion was carried out indicate the influence which this factor has upon the rate of filtration. Thus it required five minutes' perfusion for visible passage at 10 cm. pressure, one and five-tenths minutes at 15 cm. and from one-tenth to two-tenths minutes at a pressure of 25 cm.

Vital red HR, toluidin blue, trypan blue and brilliant vital red, each in 0.005 molar solution, were similarly injected into a series of capillaries. Each dye showed the same relation between rapidity of passage and capillary pressure, while increase of capillary diameter appeared to have little or no influence. The dyes tested appear to vary in the facility with which they pass through the capillary wall. Thus vital red HR is visible outside the capillary within six to ten seconds, even at pressures below 10 cm. Toluidin blue appears within a five-minute period at 8 to 10 cm., trypan blue at 12 to 13 cm. and brilliant vital red at 14 to 16 cm. Their passage is delayed by the addition of gelatin to the dye solution and is accelerated by any injury of the endothelium. These and similar observations suggest that the differences in these dyes in relation to the capillary wall are fundamentally dependent upon osmotic factors.

From these experiments it appears that increased capillary diameter has little or no effect upon the permeability of the capillary wall to these dyes. The relation between rate of passage and pressure, however, indicates the importance of changes in filtration pressure in studies of capillary permeability.

On the Intravascular Phagocytosis of Erythrocytes.—E. R. CLARK and E. L. CLARK (from the Laboratory of Anatomy, Medical Department, University of Pennsylvania). In previous studies on living cells in the transparent tails of amphibian larvæ, phagocytosis of extravascular erythrocytes by pigmented mononuclear wandering cells (macrophages) was studied, and it was found that no phagocytosis occurs until the erythrocytes have been at least fifteen hours outside the capillaries. It appeared evident that the normal erythrocyte is not susceptible to phagocytosis, but must first undergo some change.

In the present study phagocytosis of erythrocytes by the same type of cell inside the capillary was observed. The phenomenon was seen most strikingly in a tadpole which developed a condition in which about 4 per cent of the circulating erythrocytes showed, for a day or two, some visible change such as abnormal shape or deepened color. The macrophages wandering in the tissues were seen to collect around non-circulating capillaries in which were abnormal erythrocytes, to pass through the wall into the capillaries and to ingest the abnormal cells, usually remaining inside the capillary, but sometimes emigrating again. Furthermore, in one instance in which a macrophage was observed moving along the inner wall of a capillary, through which blood was circulating, it was seen that all normal appearing erythrocytes moved past the macrophage without the slightest tendency to adhere, but that every abnormal erythrocyte showed a decided stickiness toward the macrophage. Soon several such cells remained adherent to the macrophage, the circulation was blocked and the macrophage phagocytized the cells which adhered to it. Later the same performance was repeated.

It is evident that *intravascular* as well as *extravascular* phagocytosis of erythrocytes occurs, and that the susceptibility to phagocytosis is associated with a change in the erythrocyte which makes it sticky toward the macrophage.

In this as in previous studies, there was not the slightest indication of the transformation of endothelial cells into wandering cells.

Data on the Surface Composition of Cells Obtained by a Method Depending on Surface Tension.—S. MUDD and E. B. H. MUDD (from the Henry Phipps Institute of the University of Pennsylvania). The technique of a new method for the direct study of cell surfaces and some preliminary results have already been published (*J. Exper. Med.*, 1924, 40, 633, 647 and 1926, 42, 127; *Proc. Soc. Exper. Biol. and Med.*, 1926, 23, 569). The cells are observed under a dark-field microscope in the boundary surface between oil and aqueous salt solution. The cells may pass into the oil, into the saline, or may remain stable in the boundary surface. From their behavior conclusions may be drawn regarding the composition of the cell surface.

The heads of spermatozoa are extremely stable in the oil-saline

boundary surface. Neither heating, digestion with CaCl_2 or NaCl or sensitization with spermagglutinating rabbit serum appreciably alters this stability. Sperm heads are known to be composed almost wholly of nucleoprotein.

Ordinary bacteria behave much like spermatozoa. Acid-fast bacteria, however, pass spontaneously from the boundary surface into the oil, thus indicating the abundant presence in their surfaces of lipin material. Freund (*Am. Rev. Tuberc.*, 1925, 12, 124) has shown that the cataphoretic behavior of acid-fast bacteria resembles that of protein-coated particles. Undoubtedly, therefore, acid-fast bacteria have complex surfaces.

Sensitization with serum changes the acid-fast bacterial surface to one resembling protein in its behavior in the boundary plane. The sensitization is serologically specific. It is due to a deposit of the serum antibodies on the bacterial surface. The surface alteration may be reversed by treatment of the sensitized bacteria with alkali.

The acid-fast bacteria may be "defatted" by alcohol extraction. They then behave in the boundary surface like ordinary bacteria, not like acid-fast bacteria. Nevertheless, they retain their acid-fast staining properties. Acid fastness cannot, therefore, be due to an impermeable lipoid capsule, as Ehrlich supposed.

The surfaces of normal and sensitized blood cells have similarly been studied.

CORRECTION.

In E. A. Graham's article on "New Developments in our Knowledge of the Gall Bladder" in the November, 1926, number of this JOURNAL on the third line of page 641 the word "muscle" should be inserted after the word "bladder" to read, "We believe that the chief function of the gall bladder *muscle* is to maintain tonus and to prevent over distension."

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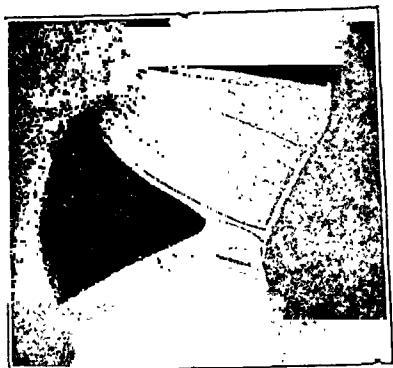
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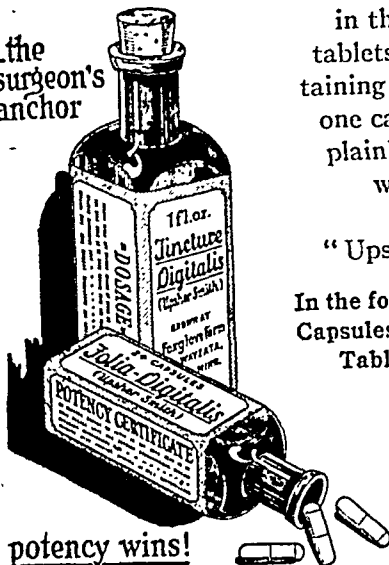
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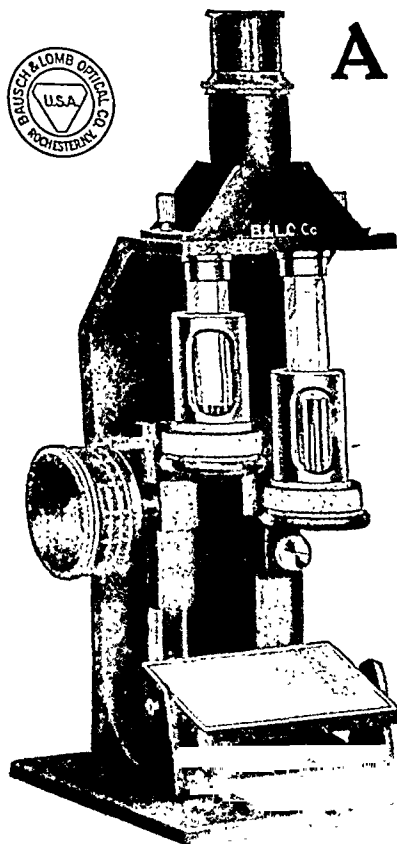
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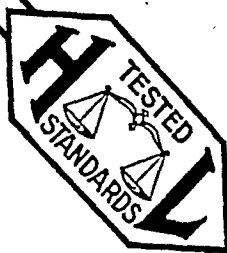
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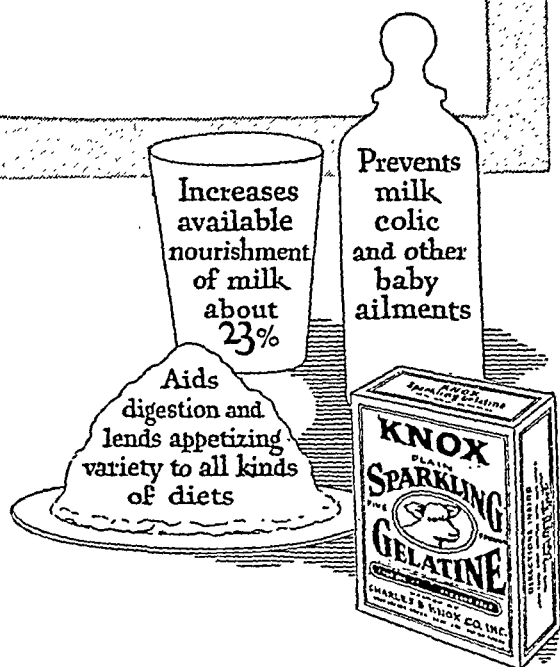
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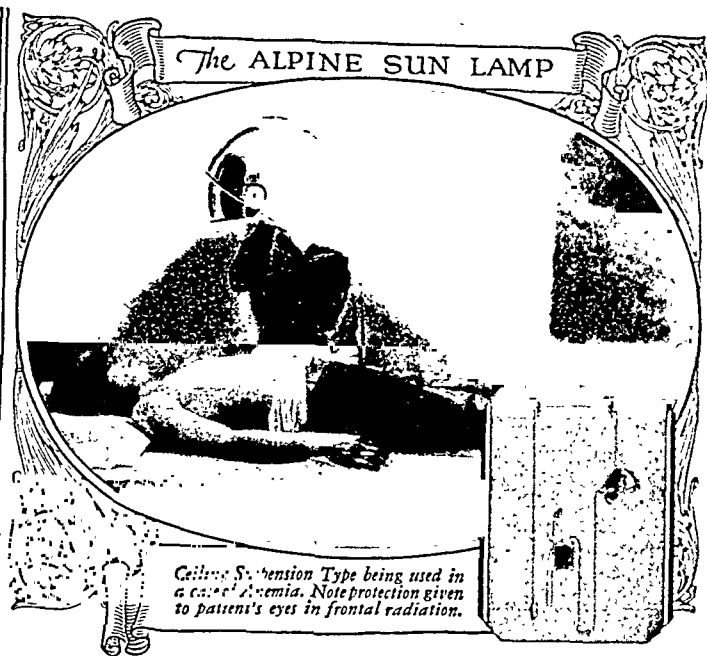
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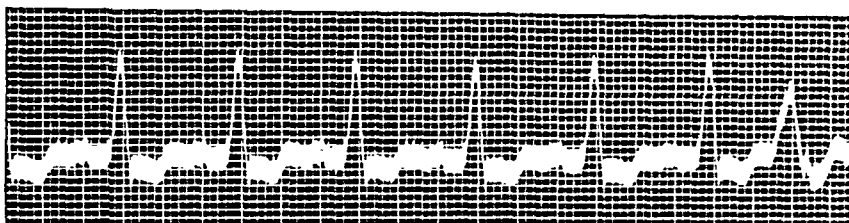
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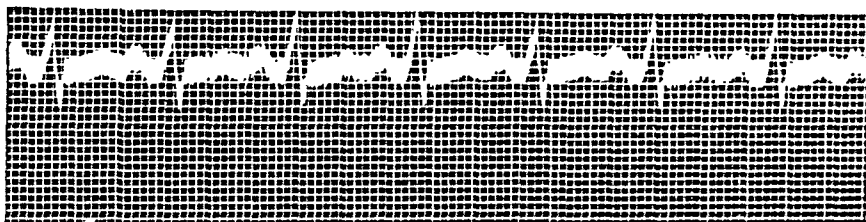
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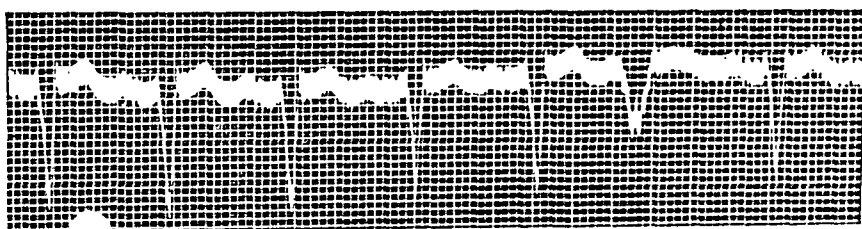
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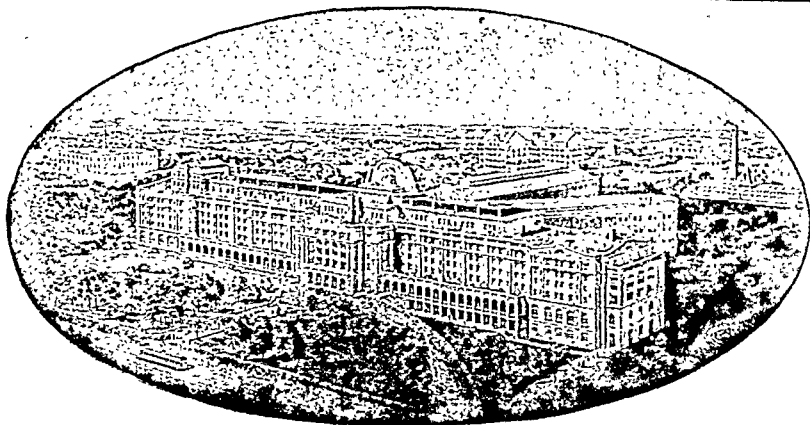
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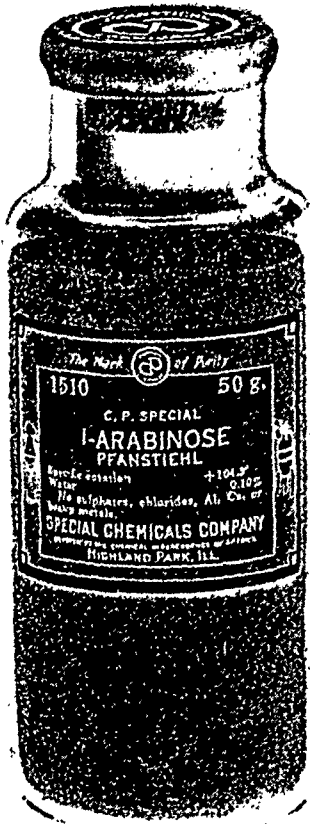
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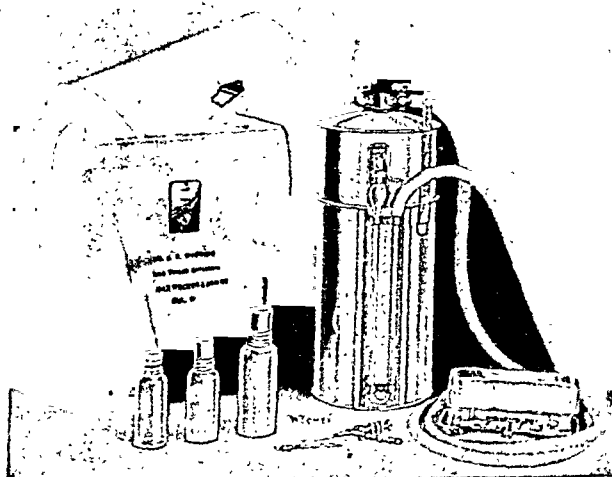
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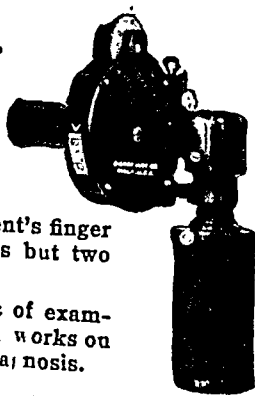


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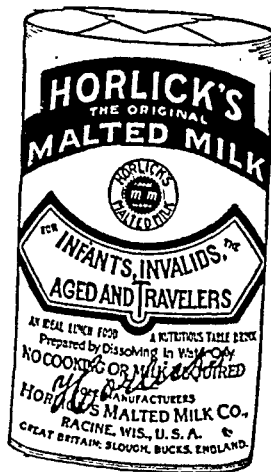


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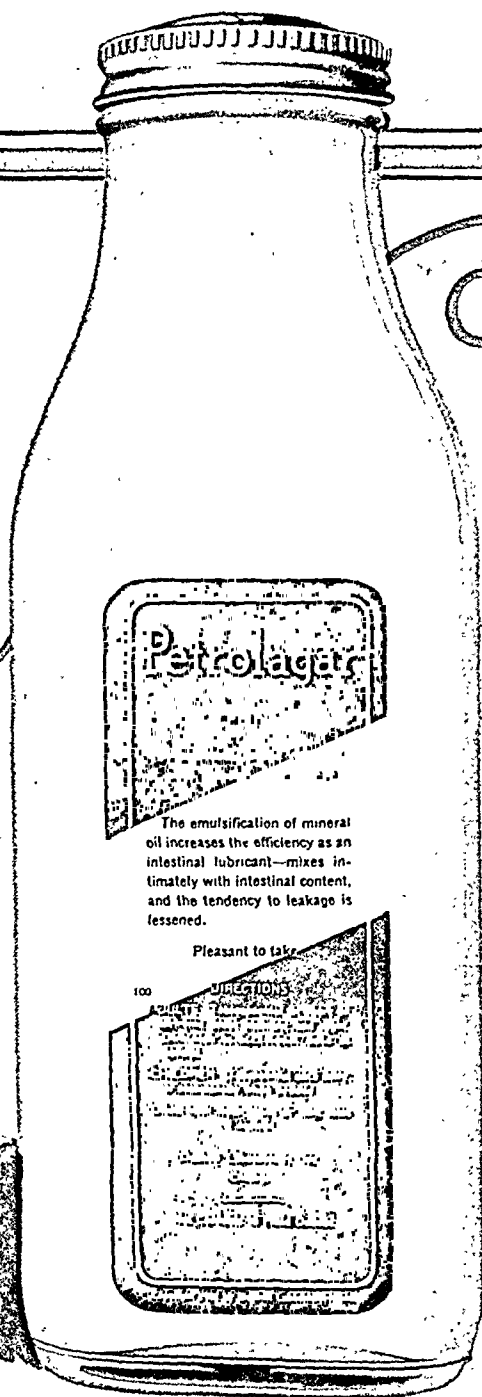
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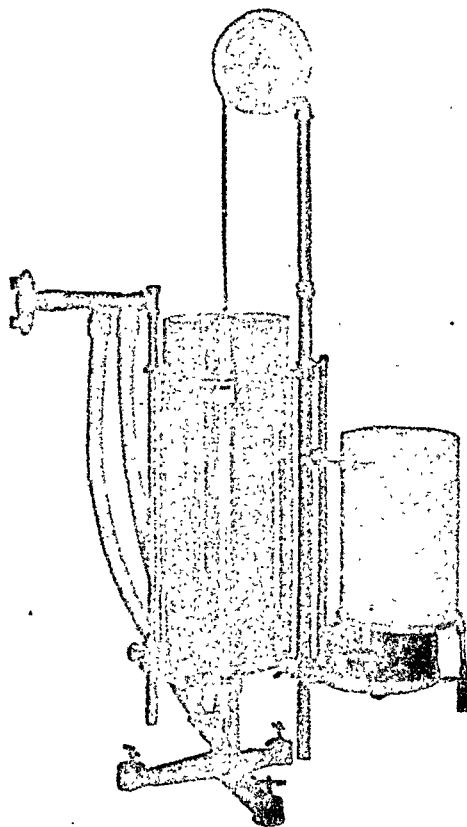
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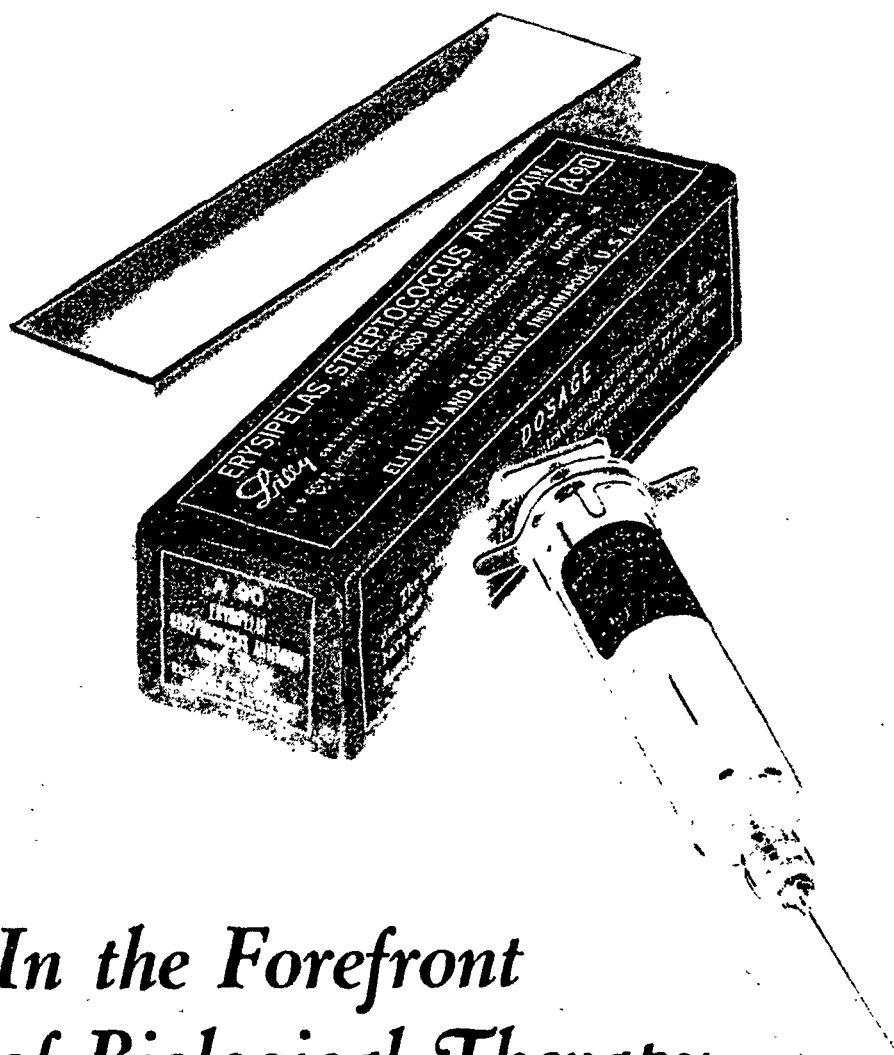
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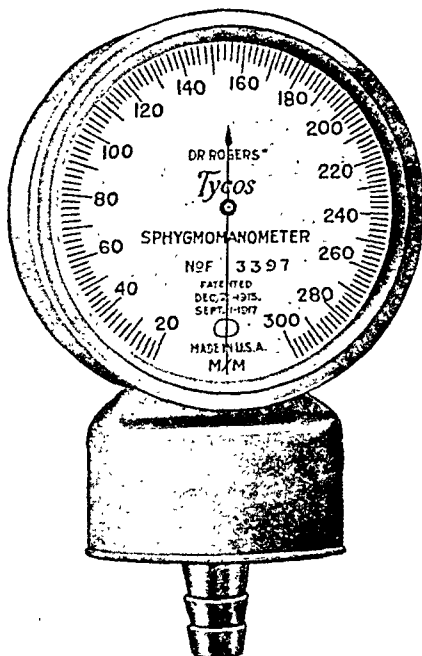
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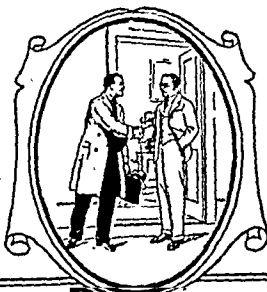
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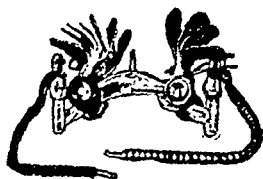
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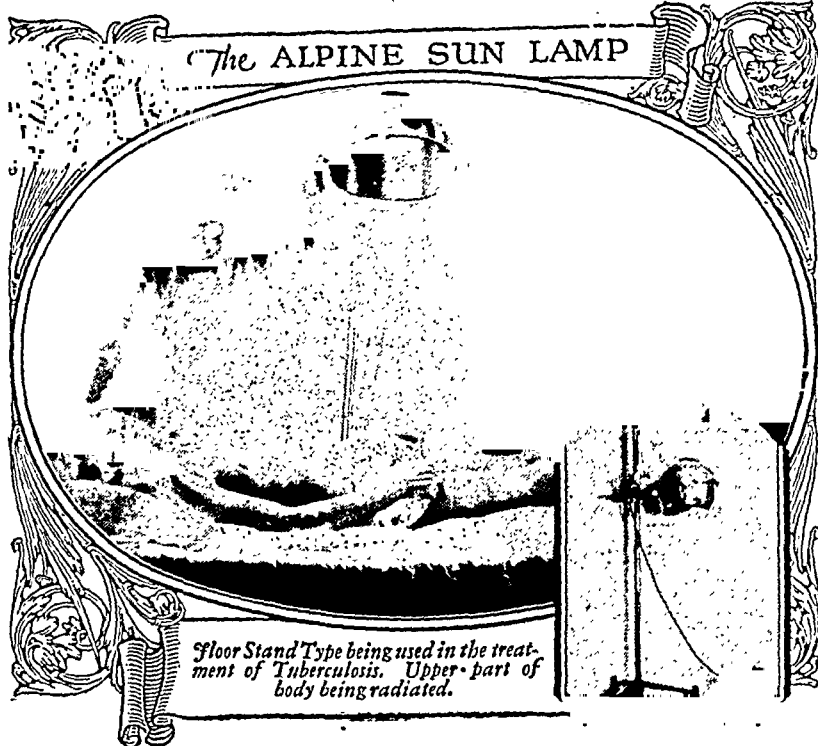
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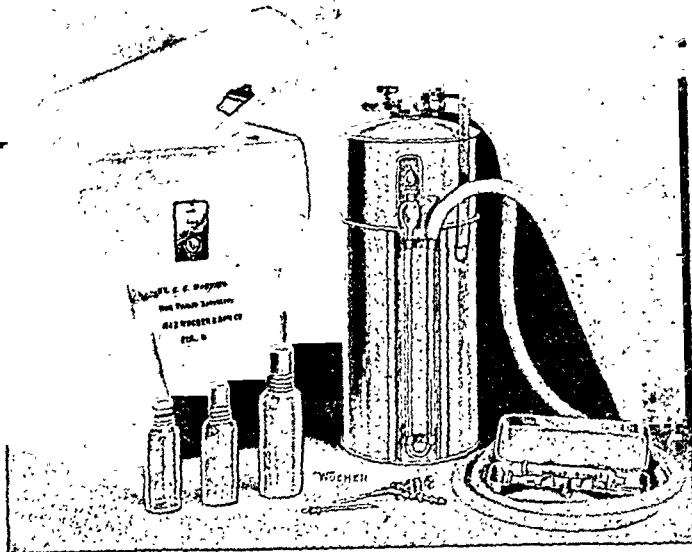
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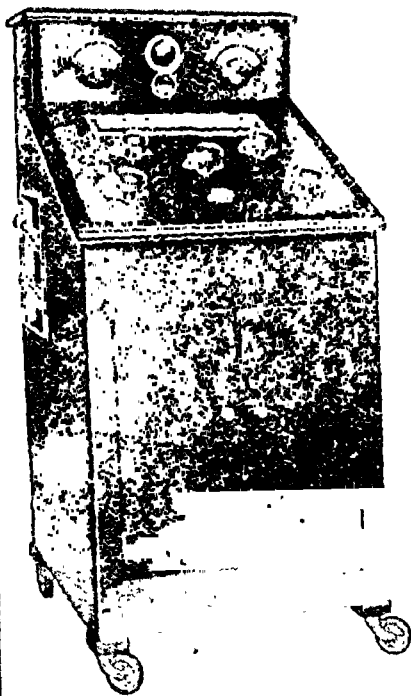
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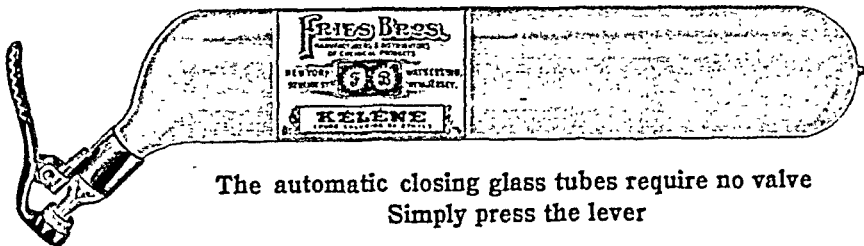
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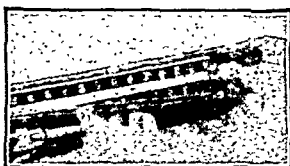
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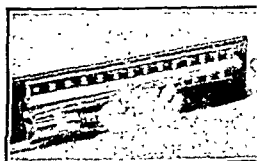
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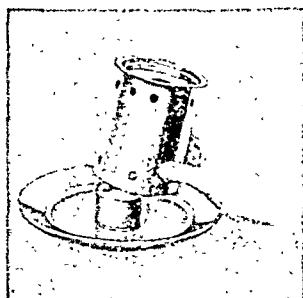
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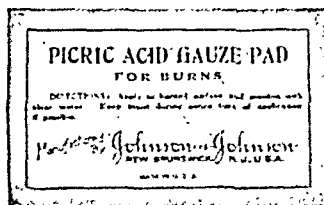
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ORIGINAL ARTICLES.

THE NEWER PHYSIOLOGY OF THE GASTROINTESTINAL TRACT.

By A. C. IVY, M.S., PH.D., M.D.

(Department of Physiology and [Pharmacology, Northwestern University Medical School.]

In this paper I desire to outline the known causes and mechanism of the gastric and pancreatic secretory response to a meal and to briefly summarize the recent advances that have been made in other fields of gastroenterology.

Gastric Secretion. The gastric secretory response to a meal can be divided into three phases with reference to the site at which the stimuli are acting: (1) The cephalic phase; (2) the gastric phase; and (3) the intestinal phase.

THE CEPHALIC PHASE. It is well established that the sight, smell and taste of food in the presence of appetite causes the secretion of gastric juice. The nervous impulses go to the stomach via the vagi.¹ According to Zoliony, a decerebrate dog will secrete gastric juice on sham feeding.² This proves that other than solely cerebral reflexes are concerned in the excitation of the gastric glands from the head region. It is certain, then, that the cephalic phase of gastric secretion is caused by (a) reflexes through the cerebral cortex (psychic), and by (b) reflexes through the thalamus, midbrain or medulla, the vagi being the sole pathway of the excitatory impulses.

THE GASTRIC PHASE. In order to study this phase without the introduction of complicating factors, we made a pouch of the entire stomach, reestablishing the continuity of the gut by a duodeno-esophageal end-to-end anastomosis.³

Mechanical Stimulation by Distention. We have found that when a balloon is placed in the pouch of the entire stomach and distended with from 150 to 300 cc. of air, the gastric glands are caused to secrete after a latent period of from five to fifteen minutes. When this stimulus is applied for half an hour from 20 to 50 cc. of the juice of high acidity is produced. The stomach of man also responds to distention, unless inhibitory factors are caused to operate.³

Chemical Stimulation by Application of Substances to the Gastric Mucosa. We have applied the common foods to the gastric mucosa in quantities insufficient to stimulate mechanically. We found that meat or meat juice is the only common food substance that stimulates on local application to the gastric mucosa. Histamin and B-alanin are pure chemical substances which stimulate on local gastric application.³

These observations show that the gastric phase of gastric secretion is caused by (a) mechanical distention of the stomach and by (b) the action on or by way of the gastric mucosa of substances in the food.

THE INTESTINAL PHASE. When a dog with a pouch of the entire stomach and a duodeno-esophageal anastomosis is fed a meal, two to four hours later the stomach begins to secrete copiously. If the meal is predigested, copious secretion begins within an hour. It is evident that in such an animal the food passes directly into the intestine from the esophagus. Therefore, the only way to account for the secretion is that it is due to the food or its digested products acting in the intestine.⁴

Since distention of the intestine does not stimulate the gastric glands, we believe that the intestinal phase of gastric secretion is due to chemical substances in the food or, preferably, that arise from digestive, and possibly bacterial action, in the intestine, which act on or by way of the intestinal mucosa.

MECHANISM. We are quite certain that several mechanisms are concerned in the secretion of gastric juice. These mechanisms are: (1) Secretory nerves; (2) increased blood flow, and (3) humoral agents. Space does not permit a discussion of the evidence supporting the first two mechanisms, but we will consider the evidence proving a humoral mechanism.

A Humoral Mechanism for Gastric Secretion. We first attempted to prove a humoral mechanism for gastric secretion by blood transfusion and long-time cross-circulation experiments. These procedures did not yield satisfactory proofs.⁵

By a method described elsewhere we were successful in transplanting a pouch of the stomach under the mammary gland.⁶ We found that when the dog was fed the transplanted pouch of the stomach secreted gastric juice. This proved unequivocally that when a meal is ingested something enters the blood stream that stimulates the gastric glands. This humoral agent must be either a hormone, or secretagogues, or both.

Pancreatic Secretion. The external secretion of the pancreas is without doubt the most important of the digestive secretions. Yet, less is known concerning the physiology of its production than of the physiology of the production of gastric juice. We have been and are at present attempting to study and analyze the causes and mechanism concerned in the secretion of pancreatic juice by methods similar to those we have used for the study of the secretion of gastric juice. Our observations indicate that the pancreatic secretory response to a meal can be divided into two phases with reference to the site at which the stimuli are acting: (1) The cephalic phase, and (2) the intestinal phase, there being no gastric phase.

THE CEPHALIC PHASE. We have repeated and confirmed Pawlow's experiments on sham-feeding a dog with a chronic pancreatic fistula.¹ The amount of secretion that results from the sight, smell and taste of food is small, amounting to only 2 cc. in fifteen minutes.

THE GASTRIC PHASE. To determine whether or not food or acid in the stomach causes the pancreas to secrete, we used a dog with a pouch of the entire stomach and a duodeno-esophageal anastomosis. A duodenal tube was passed by mouth into the duodenum for collecting secretions. We found that when various substances (acid, fat meat extract, water, and so forth) were placed in the pouch of the entire stomach no augmentation of flow of secretion from the duodenal tube resulted.

From these negative results we are lead to believe that there is no gastric phase of pancreatic secretion.

THE INTESTINAL PHASE. There being no gastric phase and the cephalic phase being so small that it is not important, the intestinal phase of pancreatic secretion is the most important phase of the external secretory activity of the pancreas. It has been definitely established that acids, neutral fats, fatty acids, soaps, proteins (meat, not egg-white), starch, alcohol, and water, stimulate external pancreatic secretion when introduced into the stomach so that they may enter the intestine. How these substances stimulate has not been definitely ascertained. Several possible mechanisms have been suggested. These mechanisms are as follows: (a) These substances, on coming into contact with the upper intestinal mucosa, excite local reflexes to the pancreas which exert either a specific secretory influence on the pancreatic cells, or cause an increase in blood flow through the pancreas. (b) These substances either contain, or on digestion yield, secretagogues that stimulate either by local reflexes, or after being absorbed into the blood, by action on the pancreatic cells or their blood supply. (c) These substances, or secretagogues which might be present in them, on coming into contact with the upper intestinal mucosa, cause a hypothetical substance, "prosecretin," present in the cells of the mucosa, to be converted into "secretin," an alleged hormone, which passes into the blood and is carried to the pancreas and stimulates it, either by direct action on the

cells or by causing an increased blood flow and capillary permeability, this being the mechanism that is commonly known as the Bayliss and Starling secretin theory. (d) These substances may effect the motility of the upper intestine which in turn, by reflexes or by an increase in blood flow, may excite the pancreas. Also a change in motility may play an indirect role by promoting the absorption of secretagogues, or the passage of a hormone stored in the mucosal cells, into the blood. Any one or all of these possible mechanisms, must be considered in analyzing how any single substance excites the pancreas to external secretion when introduced into the intestine.

A Humoral Mechanism for Pancreatic Secretion. A humoral mechanism for external pancreatic secretion has not been established. However, work has been done which has suggested that such a mechanism does exist, at least for acid stimulation.

Recently we have devised a method for transplanting the entire tail of the pancreas subcutaneously into the mammary gland.⁷ A two-stage operation was employed similar to that used by us for transplanting a pouch of the stomach subcutaneously. The transplant is entirely severed from its original blood and nerve supply. It receives blood only from the vessels that supply the mammary gland and closely adjacent structures. The transplant always takes, if a dog that has recently whelped or weaned pups is used in order to insure a vascular bed. As calculated from the amount of secretion that the transplant should theoretically produce, approximately 50 per cent of the gland transplant undergoes atrophy. But sufficient gland tissue remains to render this preparation an ideal test object for the study of many problems related to both the external and internal secretory function of the pancreas.

These transplants persist indefinitely. One is on hand now that was made one year ago. We (Farrell and Ivy) have removed the remainder of the pancreas and have found that the animal remains sugar-free on a meat diet and, that the carbohydrate tolerance, though less than normal, remains constant, constituting, we believe, a beautiful preparation for studies on problems related to diabetes.

Such a pancreatic transplant secretes a continuous secretion and is definitely excited to secrete after a meal, 6 cc. of juice having been collected in one hour. This fact unequivocally established a humoral mechanism for pancreatic secretion, because the only manner by which the transplant could be so excited would be by substances carried to it via the blood stream.⁸

This experiment does not reveal the nature of the substance, or substances, that gets into the blood. In other words, it does not show whether secretagogues in the food, or produced by digestion, are the exciting substances, or whether a hormone, or hormones, is responsible for the stimulation.

THE PROOF OF A HORMONE FOR EXTERNAL PANCREATIC SECRETION. Attempts have been made to demonstrate the presence of a

hormone in the circulating blood of animals after the introduction of acid into the lumen of the intestine. Wertheimer and Lepage,⁹ also Fleig,¹⁰ collected the venous blood from the jejunum and injected it into another animal with the result that the animal's pancreas was caused to secrete. Enriquez and Hallion¹¹ obtained a similar result from blood taken from the carotid. Popielski states that an increase in pancreatic secretion can be elicited by the injection of blood from a nonsecreting or control dog. Matsuo¹² obtained positive results in 4 out of 8 experiments in which he did an acute carotid-to-jugular cross-circulation, obviously an unphysiological type of cross-circulation. Luckhardt,¹³ using a syringe-cannula method obtained negative results on cross-circulating a secreting with a nonsecreting animal. Recently Ivy, Lim and McCarthy have found blood transfusion and cross-circulation experiments inadequate for determining whether or not a humoral mechanism is concerned in gastric secretion.⁵

We (Ivy and Farrell) have attempted to solve the problem by making the two following animal preparations: (1) A Thiry fistula of the jejunum was made in a dog that had a pancreatic transplant; (2) a 12-inch loop of jejunum was transplanted under the skin of another dog and at a later date a pancreatic transplant was made.¹⁴

It was found that when either one-tenth normal or one-hundredth normal HCl was applied to the intestinal mucosa of the loop, the pancreatic transplant would secrete copiously within four to six minutes after beginning the application. In other words, the application of a pure chemical substance to the intestinal mucosa—food and cellular detritus absent—caused the mucosa to give off something, a hormone, to the blood stream which excited the cells of the pancreatic transplant to secrete.

This, we believe, is the first unequivocal proof that a hormone may be one of the mechanisms concerned in the external secretory response of the pancreas to a meal.

It is still necessary for us to show that such a mechanism operates normally. That such a mechanism operates normally has been questioned recently by McClure¹⁵ and his associates on the evidence that the gastric chyme is rapidly neutralized in the duodenum and that the pH of duodenal contents varies from 3 to 8. This is not sufficient evidence to rule out entirely the possibility that acid chyme is causing the production of a hormone. Also, it must be kept in mind that acid chyme is being intermittently ejected into the duodenum—every three to ten seconds—and that there are brief periods, even though each period may be less than a minute in duration, of acid contact with the proximal duodenal mucosa, which when summed up may be sufficient to cause the production of a hormone.

OTHER MECHANISMS. A hormone mechanism cannot explain all of the known facts of the causes of the intestinal phase of external pancreatic secretion.

Using the Thiry-fistula-pancreatic-transplant preparation referred to above, we have found that when fresh olive oil is applied to the intestinal mucosa, either no, or a very slight amount of, stimulation of the transplant occurs. But, if we digest the olive oil with pancreatin for several days and then neutralize the acidity developed (fatty acids) and apply it to the intestinal mucosa the pancreatic transplant secretes.

Since it is known that olive oil introduced into the duodenum of a pancreatic fistula dog stimulates within a period of time (five minutes) in which it would be unreasonable to assume that appreciable digestion would have occurred, it seems very likely that olive oil stimulates on contact with the mucosa by exciting local reflex mechanisms.

We have also found that when bile is applied to the intestinal mucosa the transplant is caused to secrete. This is significant because bile passes into the intestine during a meal in sufficient quantities to stimulate the pancreas.

It should be clear from this brief discussion that several mechanisms are concerned in the causation of the intestinal phase of pancreatic secretion. A hormone is not the sole mechanism. Several mechanisms exist—factors of safety, if you please—that can arouse pancreatic secretion in achylia gastrica or in conditions in which the chyme ejected into the duodenum is not acid in reaction.

Motor Activity. The generally accepted idea regarding the effect of the vagus and splanchnic nerves on the gastrointestinal tract has been that the vagus carries inhibitory and the splanchnic motor impulses to the cardiac and pyloric sphincters, even though the reports in the literature varied. Carlson and Litt¹⁶ have shown that the response of these sphincters to nerve stimulation and to drugs depends upon the physiological condition of the sphincters at the time the stimulus is applied. If the sphincters are relaxed, the stimulus causes contraction; if the sphincters are contracted, the sphincters are caused to relax. This observation has been confirmed by Thomas¹⁷ and explains the discordant results reported in the experimental and clinical literature. It also shows that cardio-spasm, or pyloric spasm, may be due to reflexes over either the vagi or splanchnic nerves.

It was formerly believed that reverse or antiperistalsis normally occurred only in the proximal colon and abnormally in the stomach in vomiting. We know from the observations of Alvarey, Wheelon,¹⁸ Keeton, Spencer, Carlson, and the writer that antiperistalsis may occur in any portion of the gastrointestinal tract. Carlson¹⁹ has recently observed it in the esophagus in a case of esophageal stricture.

Carlson and Luckhardt²⁰ have presented evidence that hunger

contractions are due to some change in the blood. Recently we²¹ have shown that a transplanted gastric pouch shows hunger periods simultaneously with the stomach proper, evidence which unequivocally proves that hunger contractions are due to some humoral agency. It has been shown by Bulato and Carlson²² that sugar metabolism is in some way related to the humoral agency, since glucose injected intravenously stops hunger contractions and insulin administration increases hunger contractions.

Absorption. Although normally most proteins are reduced to amino-acids before being absorbed from the intestine, there are at least two protein substances that are absorbed normally from the intestine without being digested. One of these is thyroglobulin, which Hektoen has detected by immunologic methods in the blood after feeding it.²³ The other is tissue fibrinogen, as prepared by Mills.²⁴ Mills has found that tissue fibrinogen, a substance that causes coagulation of blood, can be given by mouth, causing the coagulation time of blood to decrease for several hours, and then obtained unchanged in the urine. It is well known that under certain abnormal conditions undigested protein may be absorbed from the intestine. Hettwer and Kriz²⁵ have recently made an additional contribution by finding that increased intraintestinal pressure caused by intestinal stasis may result in a sufficiently rapid absorption to cause anaphylactic shock in sensitive guinea-pigs.

The Biliary Passages. Recent investigations have at least proven that the gall bladder has one function, namely, concentration of the bile.²⁶ It also probably plays a role in the regulation of the intrabiliary duct pressure. That this is an important function in those animals that have a gall bladder is shown by the fact that the common bile duct dilates after removal of the gall bladder. Because of the small amount of smooth muscle in the wall of the gall bladder, it is probably more correct to say that the gall bladder evacuates rather than contracts.

I would like to emphasize the point that very probably the most important factor controlling the outflow of bile from the gall bladder and biliary passages is the motility and tonus of the duodenum. This has been pointed out clearly by Burget.²⁷

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OBSERVATIONS ON GASTRIC FUNCTION IN DIGESTIVE DISORDERS.

BY CHESTER S. KEEFER, M.D.,

AND

ARTHUR L. BLOOMFIELD, M.D.,

SAN FRANCISCO, CALIF.

(From the Medical Clinic of the Johns Hopkins University and Hospital.)

WITH the introduction of clinical methods of gastric analysis many years ago, it was hoped that diagnostic information of value in differentiating various disorders of the stomach would be forthcoming. The results at first seemed very encouraging and various syndromes based on studies of test meal findings were soon described. However, as time has gone by it has become evident that such supposed diseases as hyperacidity or anacidity have no very uniform pathologic basis and that great variations in gastric activity may occur in apparently normal people. Most clinicians at the present time hesitate to make an exact diagnosis from the results of gastric analysis alone.

During the past winter we have examined a series of people both with and without gastric disorders by means of a procedure,¹ which makes it possible to estimate simultaneously the volume of stomach secretions, the acidity of the pure gastric juice and the emptying time of the stomach. Our purpose was to determine critically the diagnostic possibilities of gastric functional studies. The findings in the controls have already been described;² the present paper deals with the results obtained in a series of people suffering from digestive disturbances.

Material. The material studied may be classified as follows:

1. Gastric and duodenal ulcer: There were 13 cases, 11 of which

were verified. The group was a miscellaneous one and included patients of various ages and types. In 1 case there was marked pyloric obstruction.

2. Cancer of stomach: Four cases, all advanced, verified by operation or autopsy.

3. Cholelithiasis: Five instances, all with definite biliary colic; all verified.

4. Cancer of abdominal organs other than stomach: Five cases, all verified; 2 primary cancer of liver, 2 cancer of pancreas, 1 cancer of bile ducts.

5. Miscellaneous abdominal disease: Six cases; chronic amebic dysentery, ulcerative colitis, polyposis of colon, volvulus of ileum, encapsulated peritonitis.

6. Psychoneurosis: Four cases; psychoneurotic individuals with outstanding complaint of indigestion but no evidence of abdominal disease.

A large number of cases in which the diagnosis was uncertain are not included in the present report.

Methods. The method used in studying gastric activity has been described in detail elsewhere and reference may be made to the former paper.¹ A complete protocol of a single examination is inserted here (Table I and Chart I) for reference; otherwise only a summary of the results is charted.

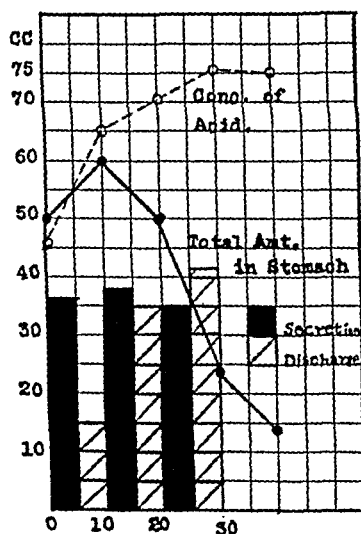


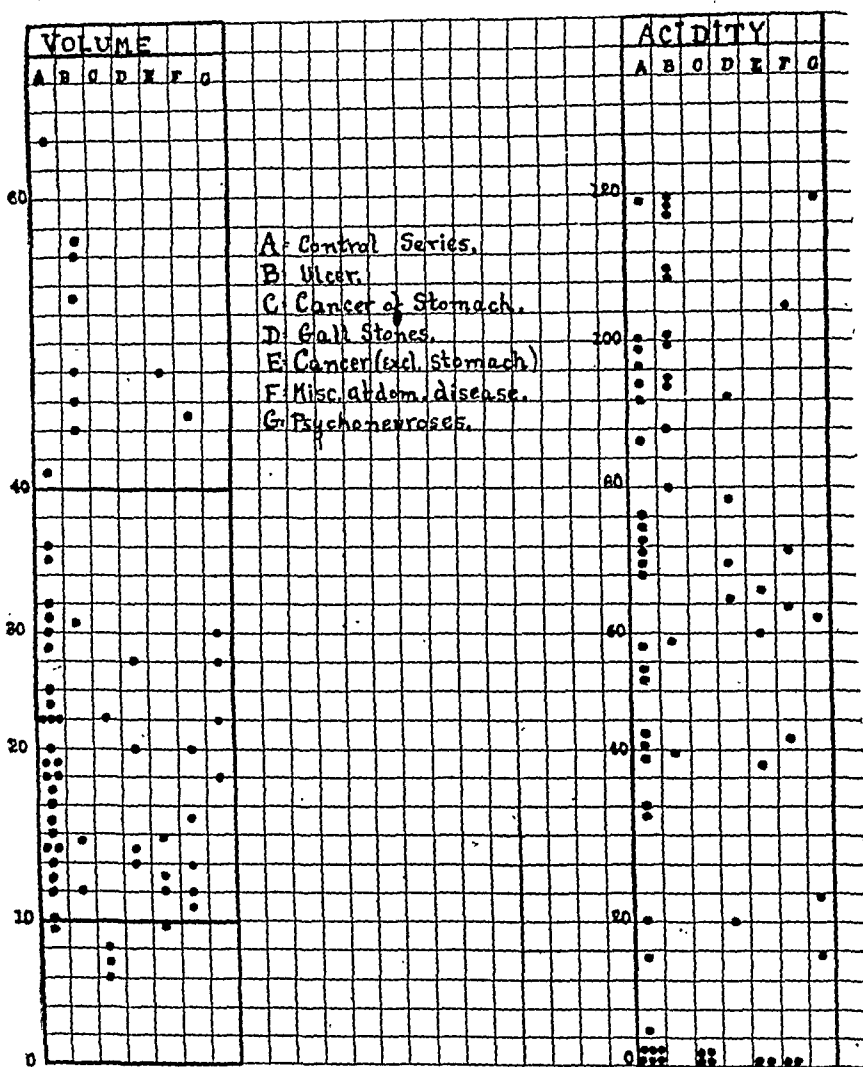
CHART I.—Findings in a normal individual.

The Volume of Gastric Secretion. In Column A of Chart II is shown the average ten-minute volume of gastric secretion in a series of controls without abdominal disorder. It is seen that with occasional exceptions the figure varies from 10 to 40 cc. In column B are shown the secretion volumes of 9 cases of gastric or duodenal

TABLE I.—SUMMARY OF FINDINGS IN A NORMAL INDIVIDUAL.

Specimen number.	pH.	Dimethyl, cc., N/10NaOH.	Phenol phthalein, cc., N/10NaOH.	Total Amount in stomach, cc.	Amount retained, cc.	Amount returned, cc.	Phthalein reading, per cent.	Amount secreted, cc.	Amount discharged, cc.
1.	1.2	52	66						
2.	1.1	52	66						
3.	1.1	60	78						
4.	1.9	10	14	50	10	40	72	35.5	15
5.	1.4	40	42	60	12	48	32	37.5	35
6.	1.2	52	60	50	10	40	16	35.0	43
7.	1.15	62	72	22	10	12	6		
8.	1.15	62	74	14	Trace		

ulcer in which satisfactory determinations were made. The large volumes of secretion obtained in 6 of the 9 cases are striking in contrast to all the other groups both normal and abnormal. It is to be noted, however, that in some of the ulcer cases, which differed in no important clinical particular from the others, the secretion was scanty. Column C shows the results in 4 cases of cancer of stomach. In 3 of these the volumes are distinctly subnormal; in



CHARTS II and III.—Secretion volume and acidity in normal and abnormal cases.

the fourth the volume was normal but not high. In the remaining four groups (D, E, F and G) the volumes all are within normal limits.

In summary, then, it may be said that the only deviation from normal which was found was the tendency to large volumes of secretion in the ulcer cases and to subnormal volumes in the instances of cancer of stomach.

The Acidity of the Gastric Juice. Column A (Chart III) shows the highest acidity of the gastric juice reached during the test (which continues over a period of approximately one hour after stimulation) in a series of controls. As we have pointed out before, there is every degree of acidity, from 0 (titratable) up to 120, although acidities of over 100 are uncommon in normal people. In column B are shown the results in 13 cases of ulcer. The well-known tendency to high acid values is brought out in contrast to

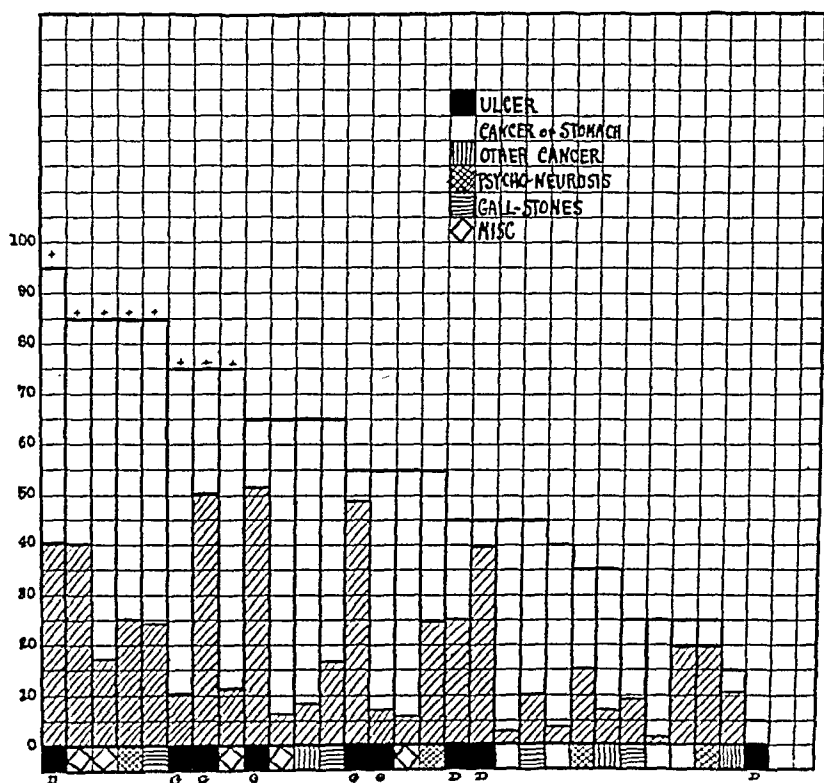


CHART IV.—Emptying time and volume of secretion in digestive disorders.

the findings in cancer of stomach (column C), which in this small series invariably showed an anacidity. In the remaining groups (D, E, F, G) there was obviously no relation between the type of disorder and the degree of acidity.

Gastric Motility. In the previous paper on gastric activity in normal people the great variations in motility of the stomach found in the various members of the group and in the same persons at different examinations were stressed. The emptying time of the stomach was found to vary over a range of from ten to ninety or

more minutes following a constant stimulus under standard conditions. Furthermore, the emptying time bore no significant relation to the volume of gastric secretion. The emptying time (minutes) in the present series of abnormal cases is shown in Chart IV. Each column indicates the emptying time in a single case, the shaded columns show the ten-minute volume of secretion (cc.) and the key at the bottom indicates the type of disease. It is immediately apparent that, just as with the controls, great variations in motility obtain in the present group. There is also no distinct relation between emptying time and any particular disease, although it may be noted that the stomach on the whole emptied more quickly in the duodenal than in the gastric ulcer cases. However, no information of any definite diagnostic value is to be deduced from these observations.

Furthermore, just as with the normal group, there were very often great variations in motility on successive examinations of the same patient (Table II).

TABLE II.—EMPTYING TIME (MINUTES) ON DIFFERENT OCCASIONS IN THE SAME INDIVIDUALS.

Case number.	Exam. 1.	Exam. 2.	Exam. 3.	Diagnosis.
148	10	20	10	Duodenal ulcer
27	40	5	..	Duodenal ulcer
150	70	20	..	Gastric ulcer
18	10	100+	..	Duodenal ulcer

Discussion. An attempt has been made to evaluate the diagnostic information which may be obtained from studies of gastric function. The present consideration confines itself to the question of volume of gastric secretions, reaction of gastric juice and motility of the stomach, leaving aside such conclusions as may be drawn from demonstration of abnormal elements in the gastric contents (blood, pus, and so forth) or from demonstration of gross food retention (pyloric obstruction).

The results indicate that on the whole the applications of gastric analysis are of restricted value. There are, however, certain findings which seem to us very useful, both from the standpoint of positive and negative diagnostic significance, provided that determinations of volume of secretion and of pH of gastric juice are made; but it should be emphasized that no picture as revealed by gastric analysis (as defined above) is absolutely characteristic of any special disease.

Ten-minute secretion volumes of over 40 cc. immediately raise a suspicion of gastric or duodenal ulcer. If the titratable acidity in the same case is high (90 or more) this suspicion becomes almost a certainty, although there are certain exceptions. Conversely, ten-minute volumes of over 15 or 20 cc. practically rule out the presence

of cancer or extensive gastritis (pernicious anemia), especially if it can be shown that the stomach can secrete acid.

Very small volumes of gastric secretions (10 cc. or less per ten-minute period) on the other hand are practically diagnostic of serious organic disease of the stomach (cancer, and so forth), especially if there is failure to secrete acid after histamine.

Aside from these findings, there does not appear to be any correlation between the results of gastric analysis and the morbid condition. We have found no picture characteristic or even suggestive of gall stones, appendicitis, gastric neurosis and other disorders. Barring the finding of pyloric obstruction, the motility of the stomach has in our hands given no clue whatever as to diagnosis.

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NOTE.—In our paper which appeared in "The Archives of Internal Medicine," 1926, 37, 819, the formula (1) on page 822 should be $[\frac{x}{y} \times A] - A =$ Maximum possible amount of juice secreted in a ten-minute period instead of $[\frac{y}{x} \times A] - A =$ Maximum possible amount excreted in a ten-minute period.

CHRONIC ULCER AND CARCINOMA OF THE STOMACH.

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RECENT revival of the discussion, with misquotations and false understanding, of the relationship of gastric ulcer and gastric carcinoma demands a restatement of our knowledge and a brief presentation of practical pathologic and clinical facts which serve to prevent and possibly cure many gastric carcinomas. It is also time to emphasize again the necessity of realizing the impossibility of differentiating, clinically, early gastric carcinoma from gastric ulcer, a fact which necessitates exploration and microscopic examination if we expect to prevent the fatal results of late gastric carcinoma by correct early diagnosis and treatment.

The evolution of our present knowledge of this subject has been dependent on increasing opportunities to study both lesions. These opportunities have changed from time to time in the last twenty-five or thirty years, at the beginning of which time all of our knowledge was based on observations of material found at necropsy, which

rarely, if ever, reveals the conditions as they are seen during life. Despite the latter fact, such material presented enough evidence to allow many authorities—Cruveilhier (1839), Rokitansky (1840), Dittrich (1848), Brinton (1856), Lebert (1878), Zenker (1882), Hauser (1882), Berthold (1883), Rosenheim (1888), Wetzoldt (1889), Duplant (1898), Hayem (1901), Fuetterer (1902) and others—to state that gastric ulcer and carcinoma occur in the same stomach;⁶ their observations and clinical histories led them to believe there might be an etiologic and a histogenetic relationship.

Clinicians, at the beginning of the twentieth century, were practically unanimous in the opinion that carcinoma of the stomach was a hopeless disease; when the lesion was palpable upon physical examination it was inoperable; gastric surgery was then in its infancy and the immediate risk of gastric or intestinal resection was so great that few surgeons dared to endanger their reputations and surgical progress in an almost hopeless task. As operative technique improved and abdominal explorations became more frequent and more successful, some of our bolder and more skillful surgeons attempted the resection of large gastric lesions. As a result of such attempts, in the first decade of this century we saw only massive neoplasms (Fig. 1, a, b). In 1909 Wilson and I studied and reported the material resected at the Mayo Clinic and stated:

"The total amount of material studied comprised specimens from 218 cases. Eight of these were from the duodenum and were all simple ulcers. The remaining 210 were from the stomach. Of these, 47 were ulcers without suspicion of carcinoma, 2 were sarcomas, 2 adenomas and 1 a diverticulum. Of the remaining 158 cases from the stomach, 5 were ulcers with enough microscopic appearance of aberrant epithelial proliferation to place them in the doubtful class as possible transition cases. Of the remaining 153 cases which were undoubted carcinoma, 109 (71 per cent) presented sufficient gross and microscopic evidence of previous ulcer to warrant placing them in a group labeled 'carcinoma developing on preceding ulcer.' Eleven other cases (7 per cent) showed considerable evidence of precedent ulcer, but not sufficient to warrant placing them in the previous group. In 33 cases (22 per cent) there was relatively small or no pathological evidence of precedent ulcer."⁹

At the time of that report all pathologic diagnoses were made on the gross and histologic appearance. There was no such thing as detailed cytology of fresh human tissue. Pathologists were still of the opinion that the cell of carcinoma was irregular and atypical with asymmetrical mitosis, and that it arose from "cut-off" epithelium. From the material which we studied and reported, we were aware of the fact that many carcinomas occurred in the borders of lesions which possessed all of the gross characteristics of simple chronic ulcer. In that series carcinoma was the condition uppermost in our minds.

In the same year (1909) I reported my observations from a study of gastric ulcers, having found changes in the cells of the tubules which permitted the following generalizations:

"While there has been a vague feeling from the pathologic standpoint that carcinoma frequently occurs upon gastric ulcer, strong pathologic evidence has been wanting. The clinician has for years noticed that carcinoma of the stomach often follows a prolonged history of gastric ulcer, and has believed that such was the forerunner of malignancy. The evidence, however, was only circumstantial. The fact established allows and demands a stronger admonition to the diagnostician, who, as soon as he has diagnosed ulcer of the stomach, must consider the strong possibility of its becoming malignant. The chances of this occurrence may readily be seen, as stated above, in the fact that 71 per cent of our resected specimens of gastric carcinoma were associated with ulcer, and that 68 per cent of our resected gastric ulcers were associated with carcinoma. . . . The question, 'Do ulcers become malignant as one of their sequelæ?' seems, from my material, at least, to be answered in the affirmative. What percentage heal, perforate or become malignant is impossible to determine."¹

In the report just quoted the generalizations were of a practical nature, and were made in the hope that more chronic gastric ulcers might be explored and resected with the possibility of removal of early carcinomatous lesions. As a result of this practical conclusion, smaller carcinomas have been removed and postoperative length of life of patients with gastric carcinoma has been prolonged.

In 1913 another report was made on a larger series, and at that time the following statement was made:

"Of 684 specimens which were either excised or resected from the stomach, 191 were chronic ulcers or ulcers in which no histologic evidence of carcinoma was present. There were 472 specimens which presented the characteristics of simple ulcer plus the presence of carcinoma, and 21 specimens of ulcer in which the presence of carcinoma was doubtful."⁵

In the literature numerous writers have made the mistake of computing percentages from such figures as those just quoted. If the reports are correctly read it will be seen that only the relative frequency of the two conditions in the resected material at hand is given; the figures have nothing to do with "the percentage of ulcers which become malignant." It is impossible for any one to tell how many ulcers of the stomach will become malignant, as I have repeatedly stated.

In 1913 Wilson wrote the following: "Thus, in between 60 and 70 per cent of the cases it is fair to say that there was found more or less pathologic evidence pointing to ulcer formation with scar tissue base prior to the development of proliferating epithelium in



FIG. 1.—*a* and *b*, Large carcinomatous lesions. *c*, Multiple chronic gastric ulcers, the larger being carcinomatous. *d*, Chronic gastric ulcer with carcinoma in the borders, the base showing only scar tissue. *e*, Chronic gastric ulcer with carcinoma in the borders and islands of carcinoma in the base.



FIG. 2.—*a*, Cells lining a normal gastric tubule from the border of a chronic ulcer *b*, Gastric tubules from the border of a chronic ulcer showing changes in the structure of the cells. *c*, Unfixed cell of carcinoma. *d*, *e*, Cells frequently found in tubules of the mucosa of chronic gastric ulcers.



FIG. 3.—Chronic gastric ulcers.

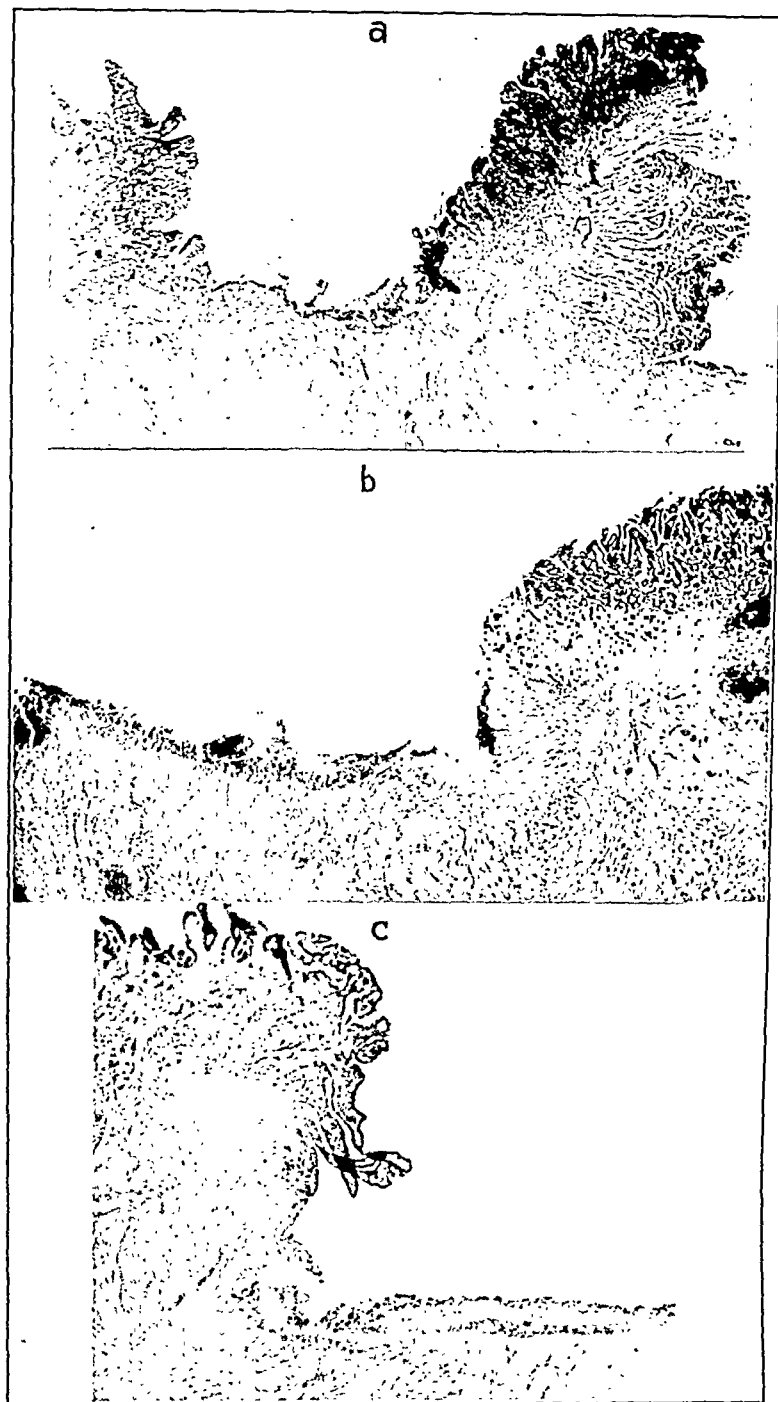


FIG. 4.—*a, b*, Small carcinomatous areas near the mucosa in the borders of chronic gastric ulcers. *c*, Extensive carcinoma in all of the coats of a gastric ulceration. The inserts show the character of the cells of the carcinoma and also intratubular cells of the mucosa (upper insert).

the area now occupied by the border of the ulcer, while in from 36 to 40 per cent of the cases such evidence is absent or inadequate."⁷

This means that in our carcinomatous ulcers there was the usual scar tissue in the craters, such as is seen in simple chronic ulcers. This scar tissue is of such density and arrangement that one would naturally suppose it to be of long standing; it is arranged in planes perpendicular to the surface of the crater; the carcinomatous cells invade this tissue.

Wilson also said: "It seems probable from a careful study of the clinical and pathologic evidence of this series of cases that gastric cancer rarely develops except at the site of a previous ulcerative lesion of the mucosa."¹⁰

In 1914 I published a report of cytologic studies of gastric tubules, and compared these findings with the cells of carcinoma. In that report it was stated that in the borders of some chronic gastric ulcers the cells in the tubules are normal in shape, being columnar and having rather small spheroidal nuclei without nucleoli (Fig. 2, *a*). Some ulcers, similar in gross appearance, may have tubules in which the columnar cells are replaced by spheroidal cells with large nucleoli (Fig. 2, *b*, *d*, *e*); these intratubular cells are frequently morphologically indistinguishable from carcinoma cells (Fig. 2, *c*). In no instance has this intratubular cytologic picture been called carcinoma, but experience has taught in a few instances that patients presenting no greater evidence of malignancy have returned with inoperable lesions after simple excision of the ulcer. This experience warrants suspicion in the presence of these cytologic changes, regardless of whether the condition is called carcinoma or not. It was this study that led Wilson to make the following statement: "Whatever may be our preconceived notions as to the relationship or lack of it between chronic gastric ulcer and gastric cancer, enough experience has now accumulated to show that we must recognize aberrant, intraglandular, epithelial proliferation as in most, if not all, cases an actual cancerous condition."⁸

In this sentence the practical clinical and economic consideration of the condition was uppermost and not an academic question of when to call a condition carcinoma and when not.

The cytologic studies already referred to have led me to make the following generalization: "Simple chronic gastric ulcers have never, in my experience, presented any visible epithelial rests which one could scientifically state were prenatal. Neither have I seen postnatal epithelial rests in the mucosa, submucosa or ulcer base that were not either composed of atrophic epithelium or real carcinoma, the latter condition being present in the base or submucosa only when there was extensive involvement of the mucosa."²

It may be stated that in a series of 967 chronic gastric ulcers the craters usually, if not always, contain no epithelial cells (Fig. 3).

. Many writers on the subject of ulcer and carcinoma of the stomach have apparently lost sight of important practical clinical generalizations in their eagerness to learn the impossible, that is, the percentage of gastric ulcers which become malignant. This impossibility has been repeatedly emphasized by the writer:

"There are two questions which have been almost constantly asked by members of the medical profession: 'Does cancer arise in chronic gastric ulcer?' and 'What percentage of chronic gastric ulcers become malignant?' These are unquestionably interesting and important inquiries, but their practical clinical significance has been greatly overestimated; the rather vicious discussion which has taken place in medical societies and in the literature has probably done some harm. Many physicians do not differentiate the things which are of purely scientific interest from those which are of practical importance. From a purely scientific standpoint, neither one of the questions as stated can be correctly answered. No one should state positively that carcinoma arises in chronic gastric ulcer until one experimentally produces chronic gastric ulcer and produces cancer in the ulcer, and then shows that all of the conditions of the experiments are comparable to the conditions which arise in human beings."⁴

"Does carcinoma develop in chronic gastric ulcer?" cannot be answered because there are no positive or negative facts regarding development visible in the study of simple or carcinomatous gastric ulcers. No one has experimentally produced a chronic gastric ulcer and then produced a carcinoma in that experimental ulcer. . . . 'What percentage of gastric ulcers become carcinomatous?' cannot be answered by virtue of the fact that it cannot be shown positively that carcinoma develops on ulcer."³

"It is important to make the diagnosis, and the differentiation of simple chronic gastric ulcer and early carcinomatous gastric ulcer cannot be made clinically. The important fact to be fully appreciated by the members of the medical profession and the laity is the common association of gastric ulcer and cancer and the present impossibility of always making a clinical differentiation."⁴

It may be seen that the writer has maintained a scientific and practical attitude toward the relation of gastric ulcer to gastric carcinoma and that what has been written has been misunderstood and misquoted. After a much larger experience (967 ulcers and 1353 carcinomas) the facts at present are:

1. Single and multiple chronic ulcerations of the stomach occur (Fig. 1, c).

2. In the case of multiple chronic ulcerations one may be carcinomatous, the rest being simple (Fig. 1, c).

3. Chronic ulcers, whether simple or carcinomatous vary greatly in size, shape and form. As a rule, most chronic gastric ulcers larger than 2.5 cm. in diameter also show carcinoma. This complication is less frequent in subacute perforating ulcers.

4. The smallest gastric carcinomas have been seen in the borders of simple chronic ulcers and not in the base (Fig. 4, *a, b*). Whenever carcinoma has been found in the base it has always been found in the borders (mucosa) (Fig. 4, *c*). The reverse of this is not always the case.

5. Studies of living and unfixed fresh cells of the gastric tubules in the borders of chronic gastric ulcers reveal the following significant and suggestive facts: (*a*) In some chronic ulcers the cells of the gastric tubules are columnar (perfectly normal) having small spheroidal nuclei and inconspicuous nucleoli (Fig. 5, *a*). (*b*) In others these cells are replaced by ovoidal or spheroidal cells with large nuclei and large nucleoli (Fig. 5, *b*); these cells are morphologically indistinguishable from malignant cells of gastric and other forms of carcinoma; in such ulcers the cells are all apparently intratubular there are no such cells visible in any other portion of the ulcer; at no time has this picture been called carcinoma, but it is considered suspicious, and wide removal seems the wisest and safest

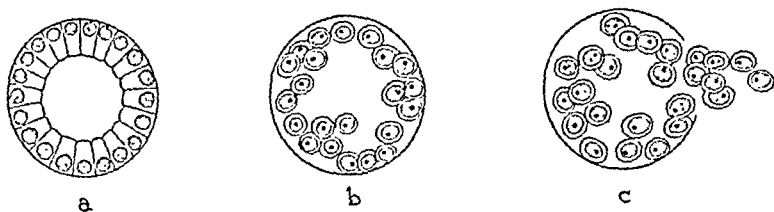


FIG. 5.—Diagrammatic representation of the cytologic variations seen in the mucosal borders of three chronic gastric ulcers: *a*, Normal. *b*, Replacement of normal epithelium by cells which have the morphology of malignant cells. *c*, The same cells invading the stroma.

procedure. (*c*) In some chronic ulcers the picture just described is found plus the presence of the cells outside of the tubules, in the submucosa, muscularis and lymphatics (Fig. 5, *c*); this picture would be called carcinoma by any competent pathologist. The preceding picture (Fig. 5, *b*), however, might well be missed by pathologists who are not cytologists and are only acquainted with postmortem or fixed and embedded tissues.

6. The relative frequency of resected carcinoma to resected or excised chronic ulcer has changed as a result of the fact that surgeons and clinicians of experience are firmly convinced of the impossibility of differentiating early carcinoma from simple gastric ulcer by any known clinical means, roentgenoscopy included. In fact, they are convinced that by clinical means other than roentgenoscopy duodenal ulcer and gastric ulcer cannot be differentiated with any degree of accuracy. Hence they resort to roentgenoscopy to determine the site of the ulcer, and if it is found in the stomach they advise exploration and excision or resection for diagnostic and therapeutic purposes.

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INFECTIOUS MONONUCLEOSIS.*

I. REPORT OF TWELVE CASES.

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THE disease which is the subject of this report, and which has received from various writers the names "infectious mononucleosis," "acute benign lymphoblastosis" and "acute lymphadenosis," was first described as a clinical entity by Sprunt and Evans¹ in 1920. It is of interest chiefly because of its unusual and, at first sight, alarming blood picture; because of its invariably favorable prognosis; because it is probably of much more frequent occurrence than has been supposed. The literature prior to 1920 contains many case reports which conform exactly to the syndrome of "infectious mononucleosis;" most of these were considered by the authors as cases of acute leukemia with recovery (Cabot,² Hall,³ Jackson and Smith,⁴ Ludke,⁵ Marchand,⁶ Turck⁷). The name "infectious mononucleosis" is here applied only because it is the one which has been most widely used in referring to this condition;

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as pointed out by Schenck and Pepper,⁸ if strictly interpreted it should imply that the "monocytes" or endothelial leukocytes are those chiefly concerned, whereas actually the characteristic cells are lymphocytes.

Infectious mononucleosis is strikingly a disease of young people; our 12 patients ranged from eighteen to twenty-six years of age, and the oldest patient mentioned in published reports was thirty-six years. Tidy and Daniels⁹ cases were between eight and thirteen and Major's¹⁰ was fifteen years. Males outnumbered females 11 to 1 in our series, and in about the same ratio in other reported series. All but 2 of our male patients were university students, several being medical students, and our 1 female patient was a pupil nurse. A certain tendency to epidemicity is seen in the time of occurrence of our cases; Case I, in 1921, is the earliest case discoverable in the records of the University Hospital; no more occurred until March, 1924, when 2 cases were admitted, followed by 1 in April, 1924. There was an isolated case in November, 1924; the months of January and February, 1925, each brought 1 case, there were 3 in March, 1925, and then no more until a case was admitted in January and 1 in April, 1926. Tidy and Daniels⁹ observed a definite epidemic in a school for boys. Practically all of our cases have occurred in the winter and spring months, when the incidence of upper respiratory infections in general is highest.

The onset is usually gradual, with the common prodromal symptoms of a general infection. Malaise, sore throat and either definite fever or sensations of feverishness were invariable as early symptoms in our series. Headache was complained of by 4, coryza or cough by 6, generalized aching and a "grippy feeling" by 3, chills by 2 and sweats by 1. Glandular enlargement was noticed by the patient at onset in 4 cases, preceding the sore throat by a day or two in 3 of them.

All of our patients complained of soreness of the throat. In 7 cases there was actual ulceration or exudation on the tonsils or pharyngeal wall; all but 1 of the others showed congestion of the fauces and pharynx in varying degrees, and that 1 was not seen by us during the height of the disease. In 6 of the 7 cases showing ulceration or exudation smears from the lesions were positive for the spirilla and fusiform bacilli of Vincent. Downey and McKinlay¹¹ state that, although some of their patients showed Vincent's organisms in their throat smears, the appearance of the throats was not that of Vincent's angina; in our cases, however, the clinical appearance and the peculiar fetid odor were certainly such as are usually considered typical of an infection with Vincent's organisms. Cultures from the throats showed the ordinary organisms, especially staphylococci and streptococci; all were negative for diphtheria.

Enlargement of the lymph nodes has been a prominent and invariable feature. It is always most marked in the anterior cervical and

submaxillary nodes, usually involving some of the posterior cervical and often the axillary, inguinal and epitrochlear nodes. In 1 case widening of the area of substernal dullness was noted, and was interpreted as evidence of enlargement of mediastinal nodes. The affected nodes vary from those barely palpable to those comparable in size to a walnut; they are firm, discrete, sometimes slightly tender but never exquisitely so. There is often, especially in the more marked cases, edema of the surrounding tissues, and slight redness of the skin. The lymphadenopathy and edema may give the neck a pyramidal contour. Sometimes only one enlarged gland is palpable in each axilla, and the epitrochlear involvement may be unilateral.

The spleen was palpably enlarged in 9 of our cases—about the same proportion as in Longcope's¹² series, and somewhat more than in most other reported series. In none of Bloedorn and Houghton's¹³ 4 cases was the spleen palpable, although it is stated that in 2 the spleen was enlarged to percussion; it may be that the incidence of splenomegaly varies in different "epidemics," and possibly, too, it is to some extent proportional to the observer's expectation of finding it. The splenomegaly is never extreme, usually slight or moderate; the spleen is firm but not excessively hard, maintains its shape, and is sometimes slightly tender. We have not noted enlargement of the liver in any case; Baader¹⁴ mentions hepatic enlargement in most of his cases, and in 1 of Longcope's¹² the liver was palpable.

The blood picture is the characteristic feature of the disease, and is usually found so on the first examination. The total leukocyte count is usually, but not invariably, increased to a moderate degree, averaging 12,000 to 15,000. Early in the disease, and during convalescence, the total number of leukocytes may be quite normal, the alteration being in the differential count. The highest total leukocyte count we have recorded was 22,400 per c.mm.; 1 of our patients had a count of 31,000 per c.mm. shortly before he came to us. The characteristic cells are lymphocytes, many of them young or lymphoblast forms, comprising from 40 to 75 per cent of all the leukocytes. The most exhaustive published study of the cytology in this disease is that of Downey;¹¹ he asserts that the blood picture is always readily distinguishable from that of lymphocytic leukemia by the cell morphology alone. The relative and absolute increase in the number of lymphocytes persists long after the subsidence of symptoms; most of our patients, when discharged as cured, still showed a lymphocytosis. That this lymphocytosis is not an individual peculiarity, a normal condition for those particular individuals, is evidenced by the fact that 4 of our patients when examined four to nineteen months after the disease had normal counts. Nor does this lymphocytosis seem to be an expression of an individual peculiarity in exhibiting a lymphocytic instead of

a polymorphonuclear reaction to an infection or other stimulus, for 1 of Sprunt and Evans¹ cases, after recovery from infectious mononucleosis, had an acute follicular tonsillitis with polymorphonuclear leukocytosis; Hopmann¹⁵ gave 1 of his patients after recovery an intramuscular injection of milk, in response to which there was the usual febrile reaction and a leukocytosis of 13,800, with 80 per cent of neutrophil polymorphonuclears.

The variation in number of cells of the granular series during the disease is less striking, but is fairly constant. Coincident with the increase of lymphocytes in the first few days of the disease, there is a decrease in the absolute number of polymorphonuclears, which may persist throughout the course. More frequently, however, the number of polymorphonuclears rises to a normal figure or slightly above normal within a few days; it may be suspected that there is an attempt at some polymorphonuclear reaction, or that this is indicative of mixed infection. The patient who exhibited the greatest increase in number of lymphocytes with a very rapid drop to a nearly normal figure exhibited also a marked coincident suppression of the polymorphonuclears, their number dropping to less than 2000 per c.mm. This circumstance is suggestive of a relationship between infectious mononucleosis and the syndrome known as agranulocytic angina.

The absence of any significant degree of anemia is striking; in 1 of our patients the erythrocyte count diminished from over 5,000,000 to 4,350,000 during the illness, but in no others was there any decrease noted. We have seen no hemorrhagic phenomena of any extent; 1 of our patients had a few petechiæ on the hard palate, and 1 gave a history of frequent epistaxis but experienced none while in the hospital. One of Downey and McKinlay's¹¹ patients had a diffuse hemorrhagic rash. The percentage of reticulocytes and the fragility of the erythrocytes were normal in the single instance in our series in which they were determined.

The findings on urinalysis were unimportant; slight transient albuminuria and the presence of a few casts or cylindroids were usual. In 1 case there was definite urobilinuria on three examinations. A number of miscellaneous laboratory examinations were made. Several blood cultures, some of them by the "massive" technique described by Fox and Leaman,¹⁶ gave only such organisms as staphylococci and diphtheroids, to which no significance was attributed. Wassermann and Widal reactions, and examinations of the blood for malarial parasites were always negative.

The temperature in infectious mononucleosis is irregular, but not "septic," ranging usually in our cases from 100° F. to 103° F., reaching 104° F. in only a few instances. This irregular fever continues one or two weeks, then gradually declines to normal; occasional rises to between 99° F. and 100° F. often continue for several days after the patient is subjectively entirely well. The subjective

symptoms more or less parallel the temperature. At the height of the disease the patients are toxic, obviously very uncomfortable, and appear very ill; the throat is painful and the enlarged glands occasion considerable discomfort; coryza, cough and headache are annoying. As the onset is gradual, so is defervescence—so gradual that it is difficult to formulate a statement of the average duration of the disease; but in most cases subjective symptoms persist for two or three weeks. It is noteworthy that objective signs—lymphadenopathy, splenomegaly and lymphocytosis—persist much longer than subjective symptoms. All of our patients when discharged were subjectively entirely well and ready to resume their customary occupations; but in many instances there was at the time of discharge but little diminution in the adenopathy, the spleen was definitely palpable and the percentage of lymphocytes increased. In the 4 cases whom we have been able to follow for some months (four to nineteen) after the disease, all these abnormal features have disappeared in a few weeks. In none of our cases has the clinical condition ever been such as to give rise to fear of a fatal termination; all our patients have recovered completely without complications or sequelæ. This invariably favorable prognosis, and freedom from complications, is commented upon by almost all writers; but Tidy and Morley¹⁷ stress the occurrence of nephritis, sometimes hemorrhagic, as a complication in some of their cases.

Acute febrile diseases with a lymphocytosis of the degree seen here are not so numerous as to give cause for the consideration of many in diagnosis. Diseases such as pertussis or Malta fever which are attended by lymphocytosis, are apt to be easily distinguishable by their characteristic clinical features. Sanders¹⁸ reports a fatal case of Ludwig's angina with 96 per cent of "lymphocytes," but suspects that the cells may really have been nongranular myeloblasts. Weichmann¹⁹ and Landon²⁰ each report a case of generalized tuberculosis with a leukemic blood picture; in the former case most of the cells were myeloblasts and myelocytes; in the latter 80 to 97 per cent were lymphocytes.

The two conditions most likely to give rise to confusion are acute lymphatic leukemia and agranulocytic angina (Schenck and Pepper⁸). In acute leukemia the total leukocyte count is usually far in excess of the 25,000 or 30,000, which appear to be about the maximum for infectious mononucleosis; leukemia is marked by anemia, purpuric manifestations and progressive deterioration; and Downey¹¹ is sure that a differential diagnosis can be made by the cell morphology alone. Agranulocytic angina, as described in most case reports^{21,22,23,24,25} is characterized by severe ulcerative angina, extreme leukopenia with almost complete disappearance of granular cells, profound toxemia and unfavorable prognosis, and occurs chiefly in middle-aged women; those features should be sufficient for a differential diagnosis. It is the consensus of opinion in this

clinic that infectious mononucleosis is identical with the classical glandular fever of children described by Pfeiffer in 1889.²⁶

The association of the spirilla and fusiform bacilli of Vincent with infectious mononucleosis is very interesting. It is frequent enough to give rise to strong suspicion, at least, of a causal relation; we have said that the organisms were found in 6 of our 12 cases, and it is described repeatedly in other case reports. The cases in which Vincent's organisms do not occur show no other difference from the case with Vincent's. We have repeatedly seen cases of Vincent's tonsillitis with only cervical adenopathy, without splenomegaly, and with a polymorphonuclear leukocytosis. We have never seen the syndrome of infectious mononucleosis associated with Vincent's gingivitis; Goadby,²⁷ however, in discussing acute (as opposed to chronic) Vincent's gingivitis, says: "In the absence of secondary infections the differential blood count shows polymorphonuclear leukopenia with a relative lymphocytosis." These factors suggest that there is some, as yet undiscovered, agent which is responsible for the disease, and with which Vincent's organisms are frequently associated, or that the combination of organisms is responsible. There is a growing suspicion, as yet not backed by any proof, that it may some day be demonstrated that acute lymphocytic leukemia and infectious mononucleosis are due to infection by the same or closely related organisms. While various organisms are always found in the throat lesions, they do not seem of such nature as to account for the disease. Coon and Thewlis²⁸ state that in a single case they isolated a diphtheroid organism from the excised tonsil and lymph node, and fulfilled Koch's postulates with the organism in guinea pigs; they give no experimental protocols, and this is the only reported instance in which culture and animal inoculation are said to have given any significant result. Whatever the causative organism may be, the indications seem clear that the portal of entry is the tonsils and lymphoid tissue of the pharynx. Thus, for the present it can only be said that the question of etiology remains unsettled.

Treatment is a simple matter, and for the most part symptomatic such as would be indicated in any mild upper respiratory tract infection. In those cases with ulcerative angina, in which Vincent's organisms predominate, we have used local applications of neoarsphenamin, 5 per cent solution in glycerin, as well as antiseptic gargles. The most effective gargles seem to be dilute hydrogen peroxid or sodium perborate solution, probably on account of their oxidizing action. In stubborn or severe cases neoarsphenamin, intravenously, seems to hasten healing of the angina. White²⁹ has given intravenous injections of mercurochrome-220 soluble in 1 case, and believes that recover was markedly hastened thereby.

Report of Cases. All cases were observed in the wards of the medical division of the Hospital of the University of Pennsylvania.

In the tables showing the hematology in each case the initial P represents polymorphonuclears; L, lymphocytes, including adult and immature forms; M, monocytes, including the cells formerly separately grouped as "large mononuclears" and "transitionals;" E, eosinophils; B, basophils. Attention is particularly directed to the last two columns in each table, representing the absolute numbers of granular and nongranular leukocytes, in contrast to the percentages; the absolute numbers are obtained by multiplying the total leukocyte count by the appropriate percentage figures.

CASE I.—A white male, aged eighteen years, was admitted, May 27, 1921. For seven days there had been bilateral, slightly tender, progressively increasing enlargement of the neck, with slight sore throat on sixth day. General symptoms were mild. Acute gonorrheal urethritis had been present for two weeks. He had lost 4 pounds.

Physical examination showed large and cryptic tonsils; an ulcer on the right tonsil; bilateral cervical adenopathy; a systolic apical murmur; the spleen was not palpable.

On June 7 a tonsillectomy under local anesthesia was done. One of the tonsils was examined histologically by Dr. Fox; his complete report appears in the accompanying paper.

On June 12 the patient was discharged in good condition.

The temperature was irregular for the first two days in the hospital, reaching a maximum of 102.4° F.; thereafter it was normal.

Laboratory findings included: Urine: Trace of albumin, an occasional hyalin cast and 15 to 20 leukocytes per high power field. Throat smear: Positive for Vincent's organisms. Throat culture: Long chain streptococci, micrococci and long rather broad rods; negative for diphtheria. Urethral smear: Positive for gonococci.

Roentgen ray of the chest showed the right hilum shadow large.

TABLE 1.—CASE I. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total non- granular per c.mm.
May 28, 1921 . . .	83	4.73	18,000	40	56	4	7,200	10,800
May 30, 1921	11,900	25	67	6	1	1	3,613	8,287
May 31, 1921	35	56	7	1	1
June 9, 1921 . . .	90	5.09	10,900	61	22	16	..	1	6,758	4,142

CASE II.—A white male, aged twenty-three years, was admitted, March 1, 1924. For one week he had complained of malaise, generalized aching, irregular fever, constipation and occasional nausea; throat slightly sore for three days.

The right tonsil had been removed, a tonsillar remnant on the left was slightly swollen; pharynx congested. There was bilateral enlargement of the anterior and posterior cervical, supraclavicular, epitrochlear and inguinal lymph nodes and of the left axillary. Soft systolic apical and basal cardiac murmurs were present. The spleen was palpable and somewhat tender.

Two days later the spleen was larger. By March 22, three weeks after

admission, he felt well, and his general condition was good, although he still had slight fever (99° F.), and his spleen was still palpable. He was discharged on that day.

The temperature was irregular, usually higher in the evening (101° F. to 102.6° F.) and in the morning down to 98° F. or 99° F. After two weeks it only once went higher than 99° F. to 99.4° F.

Roentgen ray of chest (March 5) was negative, except for abnormally extensive hilum shadows.

The Roentgen ray of the sinuses (March 14) showed doubtful increased density of the right maxillary.

Laboratory findings were: Blood Wassermann negative. Widal reaction negative. Blood negative for malaria on two occasions; on one specimens were taken every two hours from noon until midnight. Massive blood culture: Negative (aërobic and anaërobic). Urine: Very faint trace of albumin and a few cylindroids; three specimens showed a strong trace of urobilin.

TABLE 2.—CASE II. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total non- granular per c.mm.
March 2, 1924 . .	85	4.56	6,600	63	15	20*	2	..	5,290	1,310
March 5, 1924.	11,100	39	21	38	2	..	4,551	6,549
March 11, 1924 . .	88	4.51	11,100	23	72	5	2,553	8,547
March 16, 1924 . .	90	4.88	9,500	31	40	27	2	..	3,135	6,365

* Throughout the series the differential counts were made by several different observers. It is probable that some of the large, immature lymphocytes were counted as monocytes—the endothelial leukocytes. There is unfortunately now no way to rectify these errors; the leukocytes are probably best classed under two headings, granular and nongranular, as represented in absolute numbers in the last two columns of the table.

Oxidase stain of blood smear: Polymorphonuclears, 35 per cent; non-granular mononuclears, mostly large, 65 per cent. Reticulated erythrocytes, 0.5 per cent; fragility of erythrocytes, begins at 0.45 per cent NaCl and is complete at 0.35 per cent NaCl.

CASE III.—A white male, aged twenty-two years, was admitted, March 25, 1924. The onset of illness was nine days previously, with headache and feverishness. On the third day there were moderate chills, temperature of 103.6° F. and sore throat; on the fourth day enlargement and slight tenderness of the cervical lymph nodes. There was continued fever between 100° F. and 102° F.

The tonsils had been removed; the pharynx was congested. All the cervical and the inguinal lymph nodes were enlarged. The spleen was palpable.

By April 4 he was symptom free, and was discharged. At present, two and a half years later, he is in excellent health.

The temperature was irregular, ranging from 99° F. to 102° F.; it was still rising to 99° F. occasionally when he was discharged.

Laboratory findings included: Urine, faint trace of albumin and a few cylindroids. Widal reaction negative. Two blood cultures, one a massive culture; each showed *Staphylococcus albus* hemolyticus and diphtheroids in the aërobic flasks; no growth in the anaërobic.

TABLE 3.—CASE III. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total non- granular per c.mm.
March 25, 1924 . . .	95	5.03	7,100	50	46	2	1	1	3,692	3,408
March 30, 1924	10,800	26	68	6	2,808	7,992

CASE IV.—A white female, aged twenty years, was admitted, April 29, 1924. She had been ill for two days with sore throat, coryza, feverishness and generalized aching.

The tonsils were not large, but cryptic and greatly congested. There was slight anterior and posterior cervical lymphadenopathy, especially on the right side. The abdomen showed an old appendectomy scar; the spleen was not palpable.

On May 4 the cervical nodes were larger, and there was bilateral axillary lymphadenopathy; spleen palpable 4 cm. below the costal margin.

On May 14 the adenopathy was diminishing, the spleen was not palpable and the patient felt perfectly well. She was discharged in good condition on May 23.

The temperature was irregular, usually between 99° F. and 102° F., twice reaching 103° F.; entirely normal after the twentieth day in the hospital.

Laboratory findings were: Urine: Trace of albumin and a few hyalin casts and cylindroids. Throat culture: Negative for diphtheria.

TABLE 4.—CASE IV. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	Total granular per cmm.	Total non- granular per c.mm..
May 2, 1924	89	10,700	26	34	40	..	2,782	7,918
May 5, 1924	22,400	19	63	18	..	4,256	18,144
May 12, 1924	18,400	12	76	12	..	2,208	16,192
May 21, 1924	10,100	38	48	14	..	3,838	6,262
December 4, 1925 . . .	80	4.4	6,850	66	29	3	2	4,658	2,192

She was seen again on December 4, 1925, about nineteen months after the acute illness here reported, and was in perfect health. She had had an ordinary attack of grippe in December, 1924, and a tonsillectomy in June, 1925.

CASE V.—A white male, aged nineteen years, was admitted, October 20, 1924. He caught "cold in his head" at a football game; sore throat, malaise, feverishness, headache, swelling of cervical lymph nodes.

He appeared acutely ill. The pharynx was congested and swollen. The tonsils were large, with white patches on both tonsils and on the pharyngeal wall behind them. The neck near the mandible was swollen bilaterally in a pyriform shape; the swollen anterior cervical nodes seemed confluent and were tender; there was edema of the periglandular tissues. Posterior cervical nodes were discrete and swollen to hickory nut size, and there was bilateral axillary, epitrochlear and inguinal lymphadenopathy. The spleen was palpable 5 cm. below the costal margin.

On October 23 it was noted that the area of mediastinal dullness was "increased" (the measurement was not recorded).

By October 30 the throat lesions had healed, under local treatment with 5 per cent neosarsphenamin in glycerin. He was discharged on November 2.

The temperature was sustained, between 101° F. and 102° F., for six days after admission, fell by lysis in the course of three days and was normal thereafter.

Laboratory findings were: Throat culture negative for diphtheria. Throat smear loaded with Vincent's organisms. Urine: Trace of albumin and a few cylindroids.

TABLE 5.—CASE V. HEMATOLOGY.

Date.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	Total granular per c.mm.	Total non- granular per c.mm.
October 21, 1924	15,500						
October 22, 1924	14,600	45	49	6	..	6,570	8,030
October 24, 1924	18,800						
October 28, 1924	8,600	48	47	5	..	4,128	4,472
October 31, 1924	9,700	51	40	5	4	5,335	4,365
March 6, 1925	4.8	7,000	52	40	6	2	3,880	3,120

He was seen again on March 6, 1925; he had been in excellent health since discharge from the hospital. His tonsils were ragged and appeared chronically infected. The peritonsillar lymph nodes were barely palpable; there was no other lymphadenopathy. The spleen was not palpable.

CASE VI.—A white male, aged nineteen years, was admitted, January 10, 1925. He had a slight "cold in the head" for two weeks, and for five days, sore throat, malaise, feverishness, profuse sweating, frontal headache.

Physical examination showed a few petechiæ on the soft palate. Tonsils were large and inflamed, with patches of whitish exudate on them. The pharynx was congested, and also with patches of exudate. All cervical lymph nodes were enlarged and tender; one node in the left axilla and both epitrochlear nodes were enlarged. The spleen was barely palpable.

He was discharged on January 16, after several days of freedom from subjective symptoms.

The temperature was between 101° F. and 103° F. for two days in the hospital; entirely normal after four days.

Laboratory findings: Throat culture negative for diphtheria. Throat smears repeatedly negative for Vincent's organisms.

TABLE 6.—CASE VI. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	Total granular per c.mm.	Total non- granular per c.mm.
January 11, 1925	105	5.25	14,000	40	52	8	5,600	8,400
January 16, 1925	9,300	46	48	6	4,278	5,022
December 7, 1925	80	4.73	7,350	67	26	7	4,925	2,425

He was seen again on December 17, 1925. His tonsils had been removed in April, 1925; his health was excellent. There were barely palpable lymph nodes at the angle of the jaw on both sides.

CASE VII.—A white male, aged twenty-one years, was admitted, February 8, 1925. He had been ill for two weeks, first with diarrhea, tenesmus

and cramps; in the second week, no diarrhea, but coryza, sore throat and slight fever.

The tonsils were ragged, swollen and inflamed; the pharynx congested; the uvula edematous. All cervical lymph nodes were enlarged and very slightly tender, and there was bilateral axillary and inguinal lymphadenopathy. The spleen was not palpable.

He improved uneventfully and was discharged, symptom free, on February 15.

The temperature was irregular and often subnormal; the maximum was 99.6° F.

TABLE 7.—CASE VII. HEMATOLOGY.

Date.	Hb. %.	W. B. C.	P. %.	L. %.	M. %.	Total granular per c.mm.	Total non- granular per c.mm.
February 9, 1925	100	10,400	49	40	11	5,096	5,304
February 13, 1925	12,100					

CASE VIII.—A white male, aged twenty-two years, was admitted, March 9, 1925. For four days he had had anorexia, malaise, headache, feverishness, chilly sensations, vertigo on moving about and slight soreness of the throat. "Tonsillectomy" had been done at the age of seven years.

Tonsillar remnants were present on both sides; that on the right was red and swollen, with a few white spots at mouths of crypts; that on the left small but ragged and congested. The pharynx was congested. The anterior cervical lymph nodes were bilaterally swollen, and those on the right tender; there were several enlarged nodes along the posterior borders of the sternocleidomastoid muscles. One right axillary node and the right epitrochlear were palpably enlarged. The spleen was barely palpable.

The swelling of the tonsils and lymph nodes increased, and ulceration of the right tonsil was noted; the throat was treated with 5 per cent neosphenamin in glycerin. On March 17 the spleen was felt 1 inch below the costal margin. He was discharged in good condition on March 25.

The temperature was irregular; maximum, 104° F.; normal after ten days in the hospital.

Laboratory findings included: Throat culture: *Micrococcus catarrhalis*, *Staphylococcus aureus* and *Streptococcus mitis*. Throat smear positive for Vincent's organisms. Urine: Trace of albumin and a few cylindroids.

TABLE 8.—CASE VIII. HEMATOLOGY.

Date.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	Total granular per c.mm.	Total non- granular per c.mm.
March 9, 1925	5.2	6,000	41	53	4	2	2,640	3,360
March 13, 1925	12,800	26	8	66	..	3,328	9,472
March 22, 1925	9,400	21	71	6	2	2,162	7,238

CASE IX.—A white male, aged twenty-three years, was admitted, March 15, 1925. A week before admission he developed painless swelling of cervical lymph nodes, without other symptoms. For four days before admission he had sore throat, feverish sensations, anorexia, malaise, headache and slight cough with little expectoration.

The tonsils were greatly swollen, with a delicate whitish membrane on

the internal surface of each. All cervical lymph nodes were enlarged, especially on the left; there were two or three enlarged left supraclavicular nodes and bilateral inguinal and left epitrochlear lymphadenopathy. The spleen was palpable.

The throat was treated with applications of 5 per cent neoarsphenamin in glycerin, and he was given one intravenous injection of neoarsphenamin, 0.6 gm. He was discharged free from symptoms on March 25.

The temperature was irregular; maximum, 102.4° F.; normal after five days in the hospital.

The laboratory findings were: Throat culture negative for diphtheria. Throat smears at first negative, later positive, for Vincent's organisms. Urine: Trace of albumin and a few cylindroids.

TABLE 9.—CASE IX. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total non- granular per c.mm.
March 16, 1925 . . .	90	4.98	7,600	25	64.0	11	1,900	5,700
March 18, 1925	11,300	26*	71.5	2	0.5	..	2,994	8,306
March 22, 1925	11,300	34	62.0	4	3,842	7,458
April 4, 1925	6,650	38	55.0	4	2.0	1	2,727	3,923
December 8, 1925 . .	90	4.64	6,100	62	31.0	5	2.0	..	3,904	2,196

* Oxidase stain.

He returned for examination about ten days after discharge; he felt well; the lymphadenopathy had receded and the spleen was not palpable. When seen again on December 8, 1925 he was still perfectly well.

CASE X.—A white male, aged twenty-six years, was admitted, March 25, 1925. Ten days previously he developed enlargement and tenderness of the cervical lymph nodes and malaise. Two days after onset a blood count was said to have shown 53 per cent of lymphocytes. He was convalescent when admitted; he had recently recovered from severe iritis, ascribed to dental infection.

The throat was negative. There was bilateral cervical, axillary and inguinal adenopathy. The spleen was barely palpable.

He was discharged on March 27.

The temperature was normal.

TABLE 10.—CASE X. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	Total granular per c.mm.	Total non- granular per c.mm.
March 26, 1925 . . .	100	5.2	7,200	48	43	6	3	3,672	3,528

CASE XI.—A white male, aged nineteen years, was admitted, January 27, 1926. For ten days he had had bilateral swelling of cervical lymph nodes; for two days, sore throat and feverishness.

The tonsils had been "clipped;" the surface of tonsillar remnants was covered with thick greenish yellow exudate. The pharynx was congested. There was bilateral cervical lymphadenopathy, of hickory nut size, and a soft systolic apical murmur, untransmitted. The spleen was barely palpable.

He uneventfully improved, and was discharged symptom free on February 4.

The temperature ranged between 100.4° F. and 103.2° F. for two days after admission; thereafter normal, except for occasional rises to a little over 99° F.

The laboratory findings were: Throat culture negative for diphtheria; streptococci and staphylococci predominated. Throat smear positive for Vincent's organisms.

TABLE II.—CASE XI. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	Total granular per c.mm.	Total non- granular per c.mm.
January 28, 1926	90	4.69	17,000	36	57	7	6,120	10,880
February 4, 1926	5,200					

CASE XII.—A white male, aged eighteen years, was admitted, April 16, 1926. He had been subject to frequent epistaxis since childhood, much more frequent (maximum, twelve times in a week) and more profuse in the past year. Early in April he developed bilateral cervical, axillary and inguinal lymphadenopathy. For ten days he had had headache, dizziness, coryza, slight cough productive of yellowish sputum, feverishness and occasional nightsweats; for two days, sore throat; he lost 8 pounds in three months. A blood count taken April 14 (before admission) is included in the table.

The tonsils were ragged and red; the crypts contained caseous material. There was anterior and posterior cervical, supraclavicular, axillary and inguinal lymphadenopathy, bilateral; most marked in the anterior cervical group. The spleen was not palpable.

On April 22 a lymph node was removed from the neck for histologic examination; the complete report by Dr. Fox appears in the accompanying paper. He had no epistaxis while in the hospital. The slight decrease in the erythrocyte count is noteworthy. He was discharged on April 29 subjectively entirely well, but with no noticeable change in the size of the lymph nodes.

The temperature was usually between 100.4° F. and 102° F., once rising to 103.4° F.; it reached normal on the fourth day in the hospital, and thereafter occasionally rose to 99° F. or a little over.

Laboratory findings: Throat culture: Staphylococci and streptococci. Throat smear loaded with Vincent's organisms. Blood Wassermann negative. Urine: Faint trace of albumin.

TABLE 12.—CASE XII. HEMATOLOGY.

Date.	Hb. %.	R. B. C. millions.	W. B. C.	P. %.	L. %.	M. %.	E. %.	B. %.	Total granular per c.mm.	Total non- granular per c.mm.
April 14, 1926	31,000	18.0	77.5	4	0.5	..	5,735	25,265
April 17, 1926	98	5.69	21,100	22.5	72.5	3	0.5	1.5	5,170	15,930
April 18, 1926	101	5.29	19,500	29.0	66.5	4	0.5	..	5,853	13,647
April 24, 1926	8,000							
April 26, 1926	76	4.35	5,200	31.0	58.0	6	5.0	..	1,872	3,328

Platelets: 77,600 per c.mm.

TABLE 13.—COMPARISON WITH OTHER REPORTED SERIES.

Report.	No. cases.	Angina.		Vincent's +, per cent.	Splenomegaly, per cent.	Remarks.
		Congestive, per cent.	Ulcerative or exudative, per cent.			
Downey and McKinlay ¹¹	9	44	55	22	44	Throat condition not stated, 2, or 20 per cent. With coryza but sore throat not mentioned, 1, or 25 per cent; "spleen not palpable but enlarged to percussion," 2, or 50 per cent. Some cases seen too late for throat lesions.
Longcope ¹²	10	60?	20	30	80	
Bloedorn and Houghton ¹³	4	0?	75	75	0-50	
Sprunt and Evans ¹	6	16	50	0	66	
Present series	12	33	58	50	75	

Summary.—Twelve cases of infectious mononucleosis are reported; the clinical and hematologic pictures seem sufficiently distinct and definite to justify the conclusion that the condition constitutes a clinical entity.

From these cases and a review of the literature, the following are the salient features of infectious mononucleosis:

1. The usual general symptoms of an acute febrile disease of greater or less severity.

2. An increase in the lymphocytes, amounting to 40 per cent or more of the total leukocytes.

3. Lymphadenopathy.

4. Angina—either hyperemia of the fauces and pharynx, or a severe ulcerative and exudative process involving tonsils, uvula or pharyngeal wall, or all three. In the lesser grades subjective soreness may be lacking.

5. Splenomegaly.

6. The common presence of the organisms of Vincent in the ulcerative and exudative lesions.

7. Increase in the total number of leukocytes.

The prognosis is invariably favorable, and complications almost unknown.

The questions of etiology and relation to other diseases remain unsettled.

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CASE XII.—Cervical lymph node removed during late active stage of mononucleosis. The node was deep pink, homogeneous and moist. The notes taken from our laboratory description are as follows:

"Tissue is distinctly recognizable as lymph node. The capsule is wide, connective tissue is hyalin; the lymph channels of the capsule are distended and contain a pink staining clot enclosing mononuclears. The veins are similar but, of course, with distinct walls. The marginal sinus is open in places and collapsed in others. Trabeculae are not numerous and are delicate. Follicular border is present; the follicles are irregularly placed and of varying sizes. The germ centers are reasonably distinct. The central vessel is not prominent. The follicles are formed almost exclusively of quite small, normally made lymphocytes. The germ center contains the usual vesicular mononuclears. Strands and sinuses are not clearly separable. Small mononuclears are the most numerous, and indeed they probably constitute 95 per cent of the cells. The large mononuclears are of four varieties. The first is a large cell with an irregular, moderately well stained nucleus, clear nucleolus or two nucleoli; its protoplasm is lightly acidophilic. The second resembles a very large plasma cell. The third is a cell similar to the first but larger, neutrophilic in cytoplasm, phagocytic of red cells and occurs more along the sinuses—a reticuloendothelial cell. The fourth is a large vesicular cell with delicate nuclear strands and barely distinguishable cytoplasm. All these cells give the impression of being very soft, and most of them are molded to their place. Two multinucleated phagocytic cells were encountered. The nuclei in order measure: No. 1, 4 to 6 μ ; No. 2, 7 to 8 μ ; No. 3, 7 to 10 μ ; No. 4, 8 to 9 μ . There is no pigment. There are some cells with very deeply staining, homogeneous nucleus, some with a nucleus broken, which are probably degenerating small mononuclears. Mitoses are not numerous; what is probably direct division was seen once. Phagocytosis of fragments is fairly common; here and there, what seems to be a red cell, has been taken up, but polynuclears are not enclosed. Indeed, myeloid cells are exceedingly scarce. Connective tissue is delicate and not increased. There are no necroses or tubercular nodes.

Summary. A slightly hyperplastic gland with some degeneration of the small mononuclears and very marked phagocytosis by large mononuclears. There is some separation of tissue, as if by edema.

An emulsion in saline of pH 7.4 was made by gentle dabbing of the cut surface of the gland into the fluid in a dish. A drop of this was placed on a cover glass and applied to a slide prepared by the usual method for supravital staining, using a mixture of 0.8 cc. of 0.1 per cent neutral red in 10 cc. absolute alcohol to 2 cc. of absolute alcohol, to which was added 6 drops of saturated alcoholic Janus green. The slides were incubated thirty minutes before examination and reexamined five hours later.



FIG. 1.—Case XII; lymph node. Low power of field near edge showing looseness of tissue and attempt at retention of architecture.

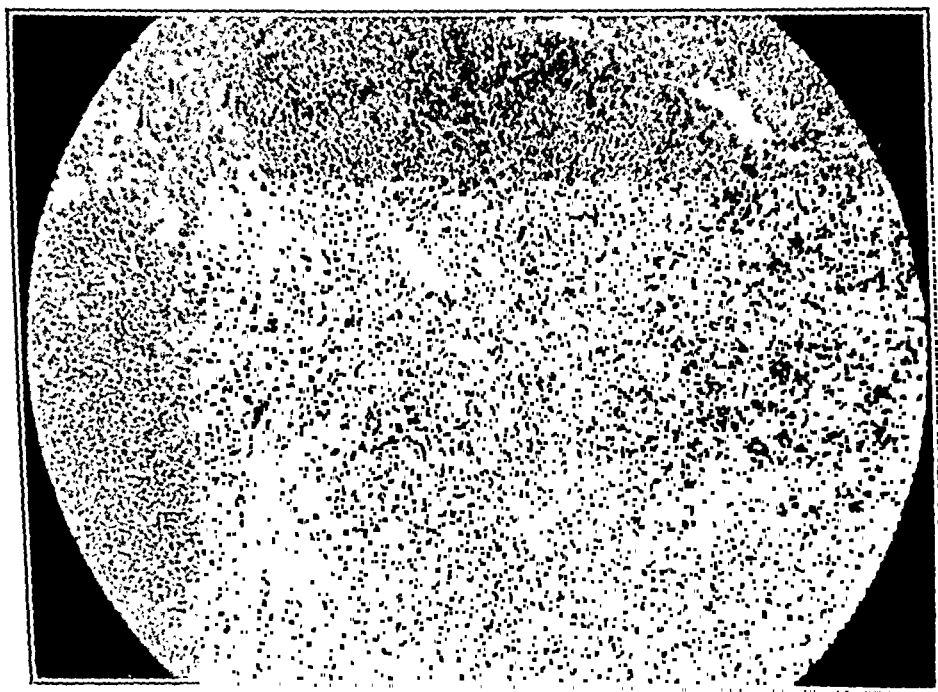


FIG. 2.—Case XII; lymph node. Follicular area with loss of normal arrangement and many loose cells in a sinus.

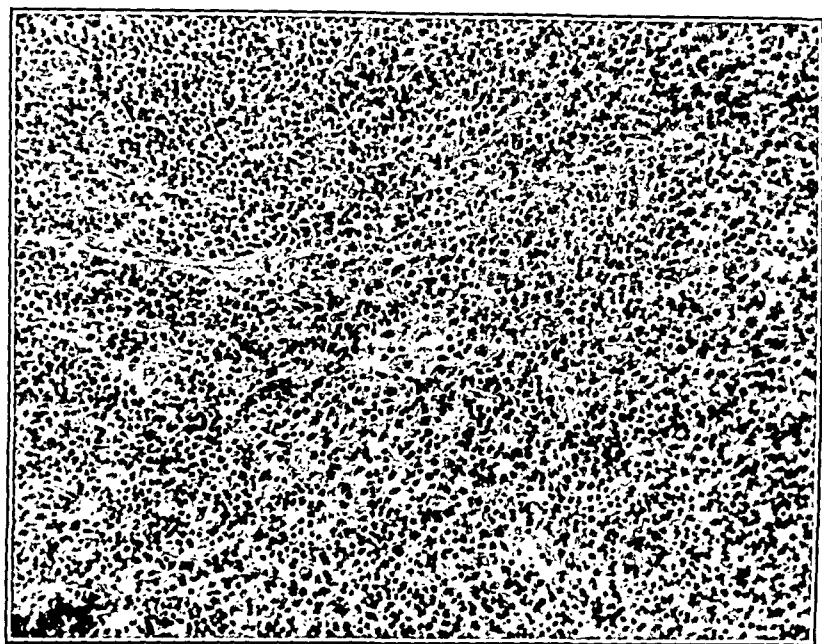


FIG. 3.—Case XII; lymph node. Closely packed cellular area with irregularly distributed large mononuclears.

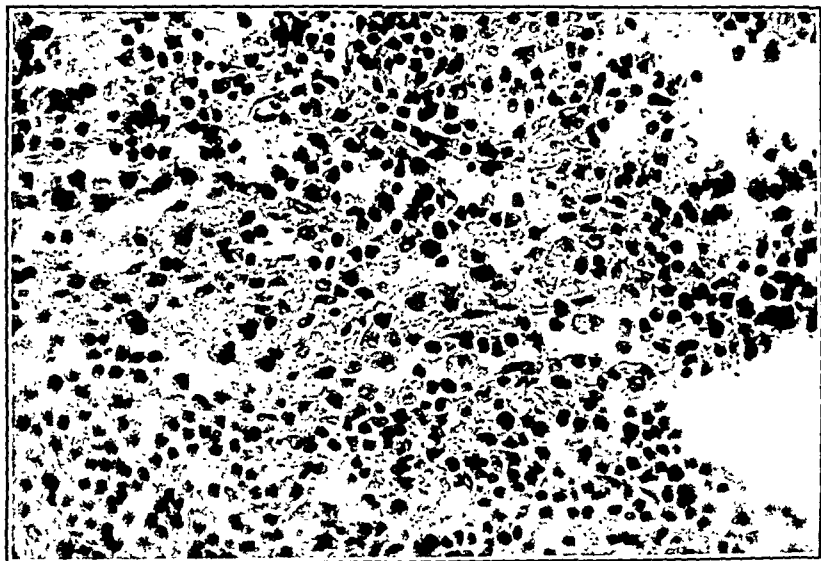


FIG. 4.—Case XII; lymph node. High power of a loose area to show relative number of large and small mononuclears.

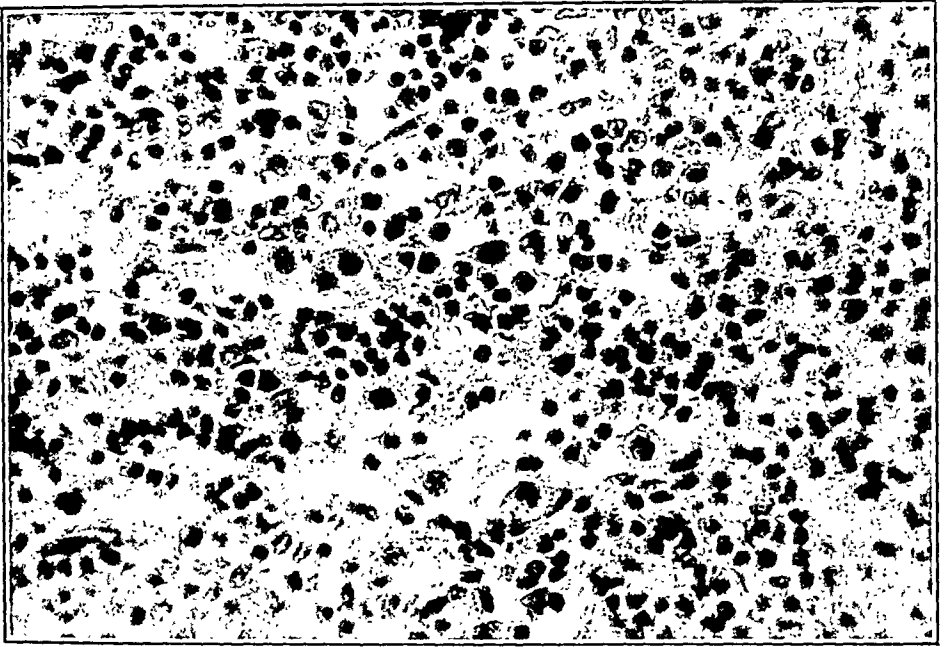


FIG. 5.—Case XII; lymph node. High power to show size, character and phagocytosis (just below middle) of large mononuclears.

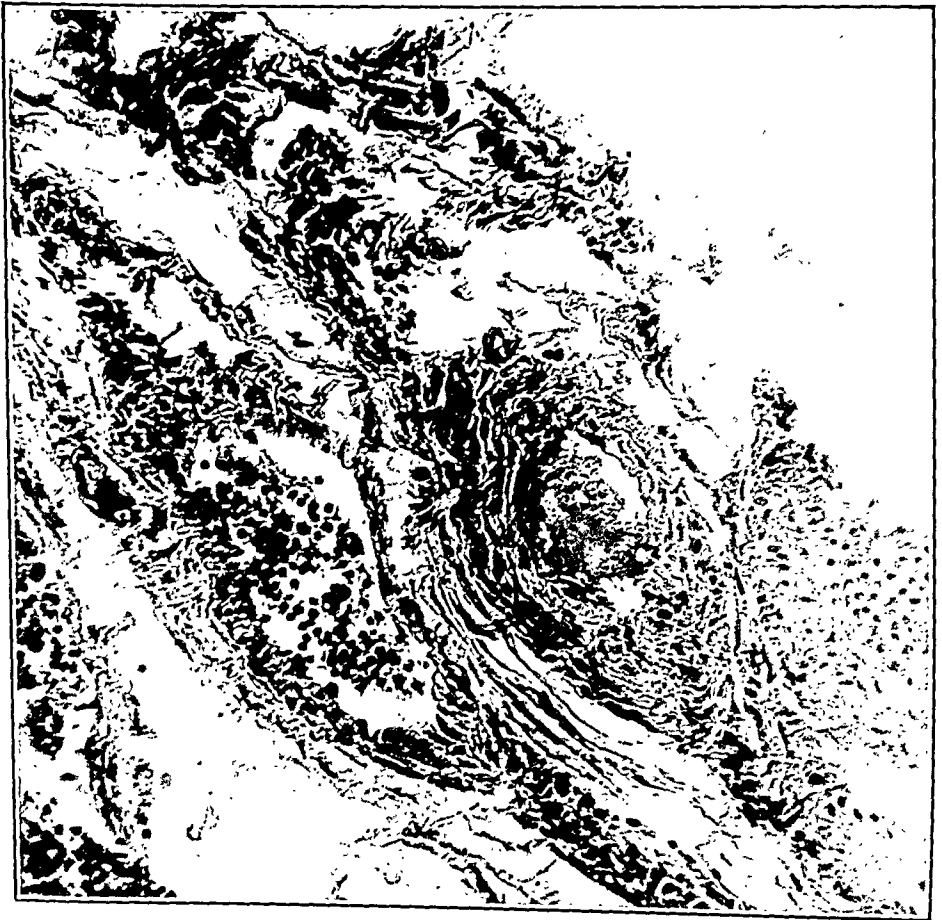


FIG. 6.—Lymph node. Dilated lymph channel in capsule of lymph node containing many small mononuclears. Vein also with recent clot.

The variation in the staining of the smallest mononuclears was quite pronounced. The large cells seemed to be the same in all fields and in all slides. All the cells seemed soft and easily compressed when lying in groups. The elements seemed to correspond to the lymphoid series in 93 per cent of the individuals. The remainder resembled clasmatocytes, polynuclears and reticulum cells. There were no monocytes, nor serosal cells, nor could any cells be found with dispersed fine granules stained by Janus green. The larger mononuclears were not entirely identic in this preparation and the histologic section, and yet close comparisons could be made.

Smears made directly from the cut surface of the gland were stained by Wright's polychrome methylene blue and by oxidase stain. Insofar as the latter is concerned, oxidase granules were found only in the occasional polynuclear and in one cell resembling a myelocyte. In the polychrome stain the elements as described in the vital staining could be identified and in the same numbers. It is noteworthy that they measured from 1 to 3 μ larger than in the supravital staining, possibly from being flattened out. The amount of cytoplasm was relatively small in all cells. Most of it was basophilic, a character best seen in the larger mononuclears of the lymphoid type. Many nuclei were neutrophilic and a few slightly acidophilic. Some nuclei were pyknotic, some broken. It seems worthy of emphasis that the small lymphoid cells in all kinds of preparations seemed soft and degenerating, if one may judge by the staining characters.

Summary. Observations on the histology of lymphatic tissue removed during the course of infectious mononucleosis and on the staining by the supravital technique of cells from a lymph node in one case are reported.

The lymphatic tissue showed marked hyperplasia, notably of the small lymphoid cells and to a less extent of the large mononuclears. Phagocytosis of fragments, but not of whole cells, was seen. The lymphocytes appeared quite soft and degenerating. By supravital staining the cells corresponded with the lymphoid elements. No monocytes were seen.

The histology of infectious mononucleosis seems not to be very distinctive, unless it be that there is a marked hyperplasia of all elements with an attempt to retain the architecture of lymph nodes. According to our tissue, however, there should be no confusion with any chronic lymphadenopathy at the height of development of mononucleosis.

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THE OCCURRENCE OF LEUKOPENIA IN HODGKIN'S DISEASE, LYMPHOGRANULOMA.

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HODGKIN'S disease, lymphogranuloma, has been separated from a host of simulating clinical pictures because clinically and, more especially, pathologically it possesses definite characteristics. Aside from the manifestations of mechanical pressure and the deformities due to abnormal glandular masses, there are often constitutional signs, that is, fever, asthenia, wasting, sweating and anemia. The blood forming organs are assailed and, therefore, we search in them for pathologic alteration and for changes in the circulating blood cells. As a rule, the red blood corpuscles suffer (but there is seldom any hemolysis*); the white cells, on the other hand, may remain normal in quantity and quality or they may range from a state of pronounced leukocytosis to a severe leukopenia.

The Leukocytes in Hodgkin's Disease. During almost any or all clinical phases of this disease the white cell count may exhibit no shift or variation in number, proportion or character. Some students, however, have tried to correlate the blood findings, particularly an increase or decrease in the total number of leukocytes or a polynucleosis or a lymphocytosis, with the stage and the condition of the disease. For instance, Bunting maintains that in cases of less than one year's duration there is no leukocytosis, but there is a relative lymphocytosis,† with an increase in the transitional cells and a fall in the number of eosinophils, while in further advanced and more generalized cases he encounters an increase in the total white cell count with a polynucleosis of 75 to 90 per cent. A relative increase in the number of large mononuclear cells, not lympho-

* Perhaps, it is permissible to infer the presence of an active process of hemolysis in what appears to be a specialized picture of Hodgkin's, so-called primary splenic Hodgkin's. I refer to the clinical syndrome of a large splenic tumor, sometimes with pain over this organ, and a delicate, but unmistakable jaundice (also itching) accompanied often by asthenia or excessive sweating with leukopenia and a relative lymphocytosis (Weber). The spleen receives the brunt of the granulomatosis alteration while the lymph glands throughout the body appear to be normal or scarcely attacked. In a number of details, the picture is unlike the usual case of Hodgkin's disease.

† It may be important to determine if Hodgkin's granuloma originates as a proliferation of lymphoid cells or of the reticular cells. The escape of lymphocytes into the running blood stream might be expected if the former were true (Symmers), whereas if the disease were primarily concerned with a stimulation of endothelial cells and the cells of the reticulum, then the absence of lymphocytes in the blood stream would not be surprising (Turnbull, Ewing).

cytes, especially the transitional type (19 to 33 per cent) was emphasized by Stewart.

The literature abounds in references to cases with leukocytosis. Fraenkel and Much, Weiss, and Fabian called attention to the rise in quantity of polynuclear cells, particularly in the later stages. Lincoln published very high leukocyte counts. Over 46 per cent of the cases of Desjardins and Ford had a white cell count above 11,000. To Bunting, a significant feature was the high percentage of transitional leukocytes found at any period of the illness, interpreted by him as caused by proliferation of endothelial cells of the lymph glands. (A leukocytosis, usually present, can also be absent in high or prolonged fever, as in the so-called Murchison or Pel-Ebstein syndrome.)

Leukopenia in Hodgkin's Disease. Fabian claims there is a normal leukocyte count or leukopenia in one-fifth of all cases. This seems a rather high percentage. At Montefiore Hospital the records of the last 18 cases of Hodgkin's disease (diagnosis established at autopsy or from biopsy) revealed a leukopenia (and this only a suggestive one) in 1 instance only (Case 9833). The patient had a total white count of 5200 at one time, a polynuclear differential of 55 per cent, with some myelocytic cells, probably due to bone marrow irritation. Some of these 18 cases were exposed to Roentgen ray, not a few had fever, toxemia and intense anemia.

We have no satisfactory conception of what produces any leukopenic state. For Hodgkin's disease, however, we can attempt to correlate, if possible, the occurrence of leukopenia with demonstrable alteration in bone marrow. At a glance it will be seen in this presentation that leukopenia was encountered in some patients whose bone marrow was definitely invaded by granulomatous tissue, and, on the other hand, in other patients when bone marrow structure remained unimpaired. No evidence is available, *pro* or *con*, as to whether the physiologic functions of bone marrow share or control the production of leukopenia or enter into its genesis whatsoever. Extreme leukopenia in Hodgkin's disease has been reported by a number of men, Gütig, Mellon, Meyer, Urech.

A. Cases with No Demonstrable Bone Marrow Changes. CASE I.—(Reported by Mellon.) *Probable Splenic Hodgkin's Disease Associated with Leukopenia (with a Relative Polynucleosis).* Mellon considered his case primary Hodgkin's disease of the spleen. The patient was a girl, aged seventeen years. She came to the hospital for a gynecologic operation, and after a few days developed fever, severe anemia and leukopenia. Within a few weeks her spleen was removed, and she showed thereafter an immediate rise of white

blood cells to 11,500. She died shortly after splenectomy. Her blood counts in detail follow:

Date (1910).	Red blood cells.	Hemoglobin, per cent.	White blood cells.	Poly-nuclears, per cent.
October 25 . . .	4,500,000	90	3,000	80.5
November 8 . . .	2,800,000	75	1,600	84.0
November 15 . . .	2,600,000	60	800	84.0
November 18 . . .	(Large spleen removed)			
November 19 . . .	2,900,000	70	11,500	84.0

Autopsy, November 19: Spleen, Hodgkin's lymphogranuloma. The liver had atrophic changes. No lymph nodes involved. Examination of bone marrow not noted.

This patient had a leukopenia before splenectomy, beginning at 3000 leukocytes and falling to 800 cells by the twenty-first day. However, there was no swing in the differential count from a polynucleosis to an agranular condition. Apparently a marked leukopenia can appear suddenly in Hodgkin's disease, albeit a rather unusual form of the disease was present here. Mellon in his article quotes the published cases of Wade and Symmers (with no complete autopsy findings) as corroboration that primary splenic Hodgkin's disease is not unknown.*

Two Cases of Widespread Hodgkin's Disease with Leukopenia (but no Agranulocytosis). Through Dr. Henry M. Feinblatt's kindness, I may cite the brief outline of 2 patients, each with extreme leukopenia (not agranular in character) during life and with well established Hodgkin's lymphogranuloma lesions at necropsy, the bone marrow showing no invasion upon careful inspection.

CASE II.—N. R., aged nineteen years, complained of abdominal distress, progressive weakness and profuse perspiration. The duration of the disease was six weeks. Gastrointestinal symptoms were marked. There was excessive perspiration afternoon and evening. Examination showed the patient to be icteric, emaciated; the chest had no evidence of tuberculosis; the liver's edge was three finger's breadth below the costal margin and the spleen was not enlarged. Fever continued between 100° F and 104° F. During observation he developed enlarged lymph nodes in the axillæ and neck. Red cell count, 3,800,000; white cell counts, 2400, 2800, 3200; polymorphonuclears, 70 per cent; hemoglobin, 70 per cent. The patient developed cellulitis of the arm and forearm and died.

CASE III.—Mr. G. was a patient, aged twenty years, complaining of gastric distress, progressive weakness and cough. He had a

* Rolleston in his Schorstein Memorial Lecture on Hodgkin's lymphogranuloma (Lancet, December 12, 1925, p. 1209) mentions briefly a case of Cornwall's, Krumhaar's case involving spleen and bone marrow (but not lymph nodes), L'Esperance's case and 2 cases considered primary splenic Hodgkin's by Ewing, (one of Donhauser and another recorded by Kummel.)

family history of tuberculosis. The course of the disease was approximately two months. It began with nausea, vomiting and progressive weakness. Examination two weeks after the onset of the symptoms revealed a slightly icteric male with a temperature of 102° F to 103° F and a rapid pulse. Cervical nodes were enlarged, lungs negative, spleen much enlarged and liver enlarged and tender. During observation there was rapid progress of the disease, with great weakness and progressive anemia. Red cell count, 2,200,000; hemoglobin, 30 per cent; white cell counts, 1400, 1600 and 1900.

A Case of Marked Disseminated Hodgkin's Disease with Extreme Agranulocytic Leukopenia and no Generalized Bone Marrow Involvement (only the Vertebral Bone Marrow was Examined; no Permission Secured for Inspection of the Rest of the Skeleton).* CASE IV.—(No. 9145.) L. R., white, male, aged twenty-eight years, was at the New York Post-Graduate Hospital in June, 1925 and had a cervical lymph node removed, which upon section pathologically confirmed the clinical diagnosis of Hodgkin's granuloma. From July 9 to November 6 of the same year he received, at the hands of a private physician, not under the auspices of the hospital, six Roentgen ray exposures, each dose and interval of treatment as follows: July 9, 1925, July 18, August 4, August 17, October 19 and November 6. At each treatment 50 cm. skin distance, 210 K.V., 4 ma. for forty minutes, using 0.5 mm. copper and 1 mm. aluminum filter; field, 10 by 15 cm. (The lymph nodes in his neck could not be felt after the third treatment.)

On December 21, 1925, he was readmitted to the hospital, complaining that during the last six weeks he had been growing steadily and rapidly weaker, that he suffered abdominal colic and that he was very constipated. He became aware of the reappearance of his neck lymph nodes, together with fever, only two weeks before readmission.

An examination disclosed bilateral cervical lymph nodes, now very large. A semiviscid exudate came from his tonsils. He seemed slightly jaundiced. His heart was not enlarged, but over its apex there was a slight soft systolic murmur. The liver and spleen were very large, and for two days before death he had signs of bronchopneumonia in his left axilla. He had continuous fever

* In this connection we wish to cite Eugen Fraenkel (Handb. d. Spez. Path. Anat. u. Hist. 1926): "(Granulomatous) nodes identical with those encountered in the spleen are found, in some cases, in those tissues closely concerned with blood formation—the bone marrow of the long medullary bones and the vertebrae. One should not fail, therefore, to investigate large portions of the skeleton. Within the medullary cavity of the severed long bones and within the spongy areas of the vertebrae, in special cases, one may discern gray opaque nodes, varying in size and number invading the vertebrae partly or entirely, sometimes so extensively that the granuloma tissue not only surrounds the dura mater but proliferates through the intervertebral foramina and so, perhaps, severely damages the spinal cord."

throughout his five weeks at the hospital, the temperature ranging from 98° F to 103° F. Laboratory tests yielded normal blood chemistry figures, a negative Wassermann reaction and an icterus index of 6. The Roentgen ray film of the chest revealed hilum thickening. A blood culture, taken a few days before exitus, contained many colonies of anhemolytic streptococci (viridans). Of particular interest were his blood counts:

Date.	Red blood cells.	Hemoglobin, per cent.	White blood cells.	Poly-nuclears, per cent.	Small leukocytes, per cent.	Large leukocytes, per cent.
December 23, 1925 . . .	3,720,000	58	4,200	76	7	8
December 29, 1925 . . .	3,120,000	49	4,450	53	45	1
January 4, 1926 . . .	4,048,000	48	7,200	66	15	13
January 11, 1926 . . .	3,192,000	51	2,800	77	3	6
January 18, 1926 . . .	2,704,000	47	900	0	55	26
January 19, 1926 . . .	2,256,000	38	240	0	51	32

Date.	Mono-nuclear leukocytes, per cent.	Disintegrated cells.	Eosinophiles, per cent.	Transitionals, per cent.	Platelets.
December 23, 1925 . . .	0	0	0	2	
December 29, 1925 . . .	0	0	1	0	
January 4, 1926 . . .	3	0	0	3	
January 11, 1926 . . .	8	0	1	5	
January 18, 1926 . . .	11	4	0	4	
January 19, 1926 . . .	10	4	0	3	79,200

At autopsy there was a disseminated Hodgkin's process, involving cervical, bronchial and abdominal nodes, liver, spleen (unfortunately no permission could be secured for inspection of bone marrow of the long bones, but the vertebræ were examined and showed no changes in bone marrow), together with multiple hemorrhagic infarctions in the lungs containing anhemolytic streptococci. Striking was the absence of any inflammatory process about these multiple lesions in the lungs. This we may interpret as a failure on the part of the patient's tissues to react to a probable preagonal bacterial invasion.

Here then (in L. R.) extreme leukopenia came suddenly, the granular cells disappearing and the total white cells falling to 240 cells within two days. Only this remarkable blood finding directed the clinician's attention to an impending death; for otherwise, despite five weeks of protracted fever of the Pel-Ebstein type, associated with Hodgkin's disease, death was not prognosticated for some time to come. In other words, clinically, there was no reason to expect him to die as suddenly as he did. The presence of fever, of a toxemia, of an anhemolytic terminal bacteriemia, the fact that Roentgen ray therapy in large doses had been employed up to six weeks before the appearance of this blood picture, not to stress the dissemination of markedly advanced Hodgkin's lesions,

each or some or all of these features may have had a part in the production of the agranulocytic leukemia.

B. Cases with Definite Bone Marrow Involvement. CASE V.—(Reported by Gütig.) *Generalized Hodgkin's Disease with Severe Leukopenia (Terminal Agranulocytosis), the Bone Marrow Showing Granuloma Alteration.* Gütig published the case of a girl, aged eighteen years, whose autopsy disclosed Hodgkin's disease of the cervical and retroperitoneal and peribronchial lymph nodes. There was also tuberculosis of the peribronchial lymph nodes and miliary tuberculosis of the spleen. She had necrosis of the tonsils, edema of the legs and an enlarged liver and spleen. The bone marrow had extensive granuloma changes. Her blood counts were:

Date.	Red blood cells.	Hemoglobin, per cent.	White blood cells.	Poly-nuclears, per cent.	Lymphocytes, per cent.	Myelocytes.
September 27	800	60.0	40.0	
October 3	1,700,000	25	850	51.0	48.0	1
October 8	1,050	70.0	30.0	
October 16	1,040	35.0	64.0	
October 24	1,200,000	20 to 25	950	45.0	55.0	
November 2	700	50.0	50.0	
November 3	1,320,000	20 to 25	680	55.5	44.5	
November 8	700	65.5	34.5	
November 14	1,940,000	20 to 25	880	55.0	45.0	
November 18	1,060,000	..	1,200	1.0	99.0	
November 19	1,000,000	..	2,000	0.0	100.0	

The total white cell count, constantly low, toward the end suddenly made a feeble attempt to rise as the granular white cells vanished from the blood stream. In this case, also, the presence of necrotic tonsils provokes the suspicion that the agranulocytic state accompanied an unappreciated clinical condition of agranulocytic angina, in which, as a rule, the red blood cells and hemoglobin suffer little, if any. Gütig's patient, however, had a marked anemia with or from Hodgkin's disease, so that the reduction in hemoglobin and red blood cells would militate against the diagnosis of a possible agranulocytic angina. Vincent's angina is not mentioned in this case.

Gütig tried to produce a postprandial leukocytosis, giving his patient food during the leukopenic state while as yet no agranulocytosis had appeared. (On November 11; see table above.) The leukocytes did not increase in number. This suggestive experiment may offer a means of gauging whether or not the white-cell-forming tissues still retain their capacity to produce additional leukocytes, as noted in the blood stream, however severe a leukopenia there may be. As is well known, from the intravenous introduction of protein or bacteria there is a sudden leukopenia. This phenomenon is interpreted as an excessive depositing of leukocytes into the capillaries of the tissues of the body, so that in the blood there is a lessened number. Obviously, a postprandial leukocytosis response

could be expected in this kind of leukopenia, while in the leukopenia associated with a severe aplastic condition leukocytes would not be plentiful in the various tissues of the body.

Gütig's report resembles a case in our own experience and has particular value for us because he published a detailed description of the bone marrow changes.

CASE VI.—A Patient with Generalized Hodgkin's Disease Accompanied by Leukopenia, the Bone Marrow Exhibiting Extensive Granuloma Lesions. (No. 1226.) J. T. was admitted to the New York Post-Graduate Hospital, April 19, 1926, and died, May 3, 1926. He was a vigorous and well built Polish man. Quite suddenly he felt prostrated, developing drenching sweats, abdominal colic and attacks of diarrhea. He had bilateral cervical adenitis (he knew of these enlarged glands for six weeks only), right axillary nodes, large left axillary nodes, a large liver and spleen, moderate edema and his blood was anemic, with some tendency to leukopenia. An excised lymph node was diagnosed pathologically as Hodgkin's disease.

After a four weeks' absence he was readmitted to this hospital. His symptoms were aggravated. It was apparent at once that his pallor and edema were increased and that now he had ascites and bilateral hydrothorax. Despite this fluid accumulation, he had lost body weight and he was beginning to develop pronounced signs of cardiac insufficiency. The severe anemia remained unchanged and uninfluenced. His neck and axillary lymph nodes were not large, his liver seemed smaller and the size of his big spleen unchanged. Fever developed and remained during his last days in the hospital, but no leukocytosis was noted.

A study of his blood counts demonstrated that, in addition to a marked secondary type of anemia (there being anisocytosis and moderate poikilocytosis), his leukocyte cells remained low, exhibiting a tendency toward lymphocytosis with thrombocytopenia during the early days after his readmission to the hospital. He did not rally after two blood transfusions, the anemia remaining unaffected. A week prior to his death his leukocytes tried to mount and shift toward a relative polynucleosis. The blood counts were:

Date (1926).	Platelets.	Red blood cells.	Hemoglobin, per cent.	White blood cells.	Poly-nuclears, per cent.	Small lymphocytes, per cent.	Large lymphocytes, per cent.
February 3 . . .	102,000	3,456,000	62	5,000	40	28	25
February 16	3,088,000	65	3,600	50	30	10
February 18 . . .	140,000	3,712,000	62	5,200	25	27	30
February 25	3,448,000	60	3,400	37	39	17
March 5 . . .	218,000	3,904,000	60	4,400	36	27	24
March 8	3,368,000	59	3,400	36	34	21
April 19 . . .	89,300	2,384,000	48	1,600	31	40	24
April 27	1,152,000	20	2,400	60	24	11
May 3	1,016,000	20	3,000	50	25	19

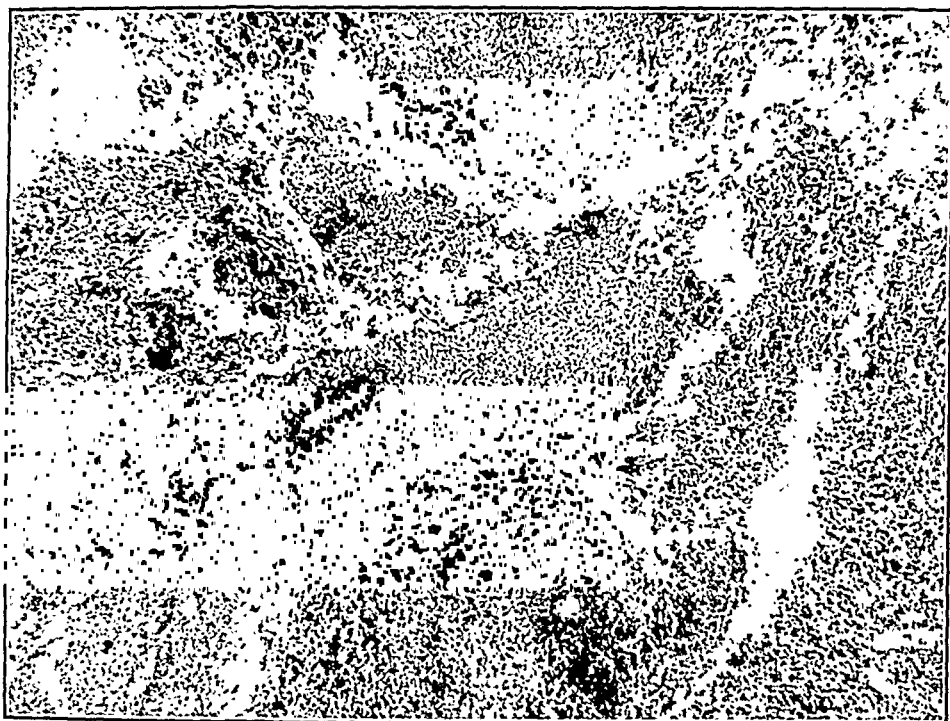


FIG. 1.



FIG. 2.

Date (1926).	Mono- nuclear leuko- cytes, per cent.	Disinte- grated cells, per cent.	Eosino- phils, per cent.	Baso- phils, per cent.	Transi- tionals, per cent.	Normo- blasts, per cent.	Myelo- cytes, per cent.
February 3 . .	5	..	1				
February 16 . .	6	2	.	.	2		
February 18 . .	3	15					
February 25 . .	5	2		
March 5	10	3		
March 8	5	2	.	1	1		
April 19	5						
April 27	1	3	2	1
May 3	3	3	.	1	2	3	

J. T.'s necropsy disclosed a generalized Hodgkin's lymphogranulomatosis involving all nodes, the spleen and the bone marrow (Figs. 1 and 2). In addition there was an old tuberculous process of the peribronchial lymph nodes, an extensive ulceration of the laryngeal mucosa, a generalized edema and an early bilateral lobular pneumonia. His bone marrow, microscopically, showed a fairly good proportion of eosinophilic and neutrophilic myelocytes and leukocytes, but the marrow substance was rather poor in erythroblasts and erythrocytes and an occasional mitotic macroblast was seen. Numerous megakaryocytes and giant cells resembling the Dorothy Reed type were present. Very extensive areas of granulation tissue and of necrosis similar to those in the lymph nodes and spleen were seen. Some giant cells of the megakaryocytic type were observed, but it was difficult to decide whether they belonged to the granulomatous areas or to the elements of the bone marrow.

Discussion. Just what produces so severe a depletion of white cells in the circulating blood is not clear. For its explanation a variety of reasons has been advanced, namely, a prolonged or advanced toxemia, protracted or excessive Roentgen ray treatment, actual lymphogranulomatous infiltration replacing the erythroblastic tissue, thus causing an eventual aplasia; also arsenic therapy has been held responsible for producing bone marrow exhaustion after an initial stimulation.

Pathologically, Hodgkin's disease is an encroaching, spreading process, whereby the lymph structure (of glands, and so forth) is replaced by chronic granulomatous tissue. The lesions show, microscopically, proliferated endothelial cells, peculiar, large giant cells, eosinophilic cells, in fair numbers, overgrowing connective tissue, and clusters of lymphoid cells. These latter are, possibly, residual normal areas in lymph nodes, now almost completely invaded by granulomatous tissue; or they may represent collections of lymphoid cells gathered from the blood stream. Regardless of whether or not the pathologic process is barely visible or palpable for the clinician or clearly widespread, many authorities believe Hodgkin's granuloma always a disease of the entire lymphatic system and

blood forming organs. In most, or nearly all, cases the bone marrow is spared. However, there are instances when a depression of all the blood elements is attributable to an aplasia (nonregenerative state), paralyzing the bone marrow functionally, or else altering it to such a degree, by actual granulation tissue invasion, that the bone marrow no longer regenerates any myeloid forms. An agranulocytic white cell blood picture can, therefore appear. In Kraus-Brugsch (*Spez. Path. u. Therap. inn. Krankh.*, vol. 8) Naegeli described a case of chronic lymphatic disease, and neither in the blood nor in the histologic section of the patient's organs could he find any neutrophilic cells, indicating, to his mind, that the agranulocytosis was caused when the myeloid-cell-producing tissues were overwhelmed by the lymphatic disease.

1. *Aplasia.* An aplasia, consequently, may lead to a leukopenia, agranulocytic in type. Sometimes the blood's white cells are greatly diminished in number, and there is widespread alteration in the blood-forming tissues. For want of more precise knowledge, it is surmised that the toxin of certain diseases can do this, for example, typhoid, measles (during the incubation period), very severe pneumonias and chronic granulomatous inflammatory processes, such as tuberculosis, leprosy, syphilis, chronic glanders, actinomycosis, blastomycosis, streptothrix infections, mycosis fungoides, sporotrichosis. It is sheer speculation to assume that a leukopenia in these conditions is the result of an inhibiting or paralyzing effect of toxin upon the white blood cells in the blood stream or that the white cells are found in the blood stream in such meager numbers because toxin has directly affected the bone marrow, causing a so-called "insufficiency of the bone marrow" in a physiologic sense. (An anaphylactic leukopenia has been described, but has no particular bearing here.)

2. *Toxemia.* Whether in Hodgkin's disease we are dealing with an infection and its toxin or with a neoplastic process or, possibly, with a condition which partakes of the characteristics of infection and newgrowth is, of course, unknown. At all events it is not outside the bounds of possibility that a pronounced leukopenia in this disease may be caused by such an, as yet, undiscovered poison affecting directly the white cells in the blood stream or paralyzing the white cell response of the bone marrow. The cases cited in this text may illustrate and lend support to this conception. However, granulation-tissue invasion into the bone marrow does take place in some cases and a leukopenia present in this connection might be directly related to the bone marrow disease. Cases V and VI have bearing upon this point.

3. *Effect of Roentgen Ray.* Confusion exists as to the influence of Roentgen ray treatment in the production of leukopenia. Experimentally, Murphy and Sturm pointed out the destruction and subsequent proliferation in the germinal centers of lymph glands exposed

to Roentgen ray. They found an immediate leukopenia with pronounced lymphocytosis within a day or two after exposure and following this a gradual but well established leukocytosis by the tenth or fourteenth day. With excessive doses these workers could severely damage the germinal centers, whereupon the initial leukopenia lasted a number of days until the quickly ensuing death of the animal. For human beings we could find no clarified reports concerning the effect of Roentgen ray upon normal blood counts. The influence of Roentgen ray upon the white blood cells in diseases like leukemia is recognized, although not understood (Minot, Levin), and in the practical therapeutic use of Roentgen ray the danger of white cell depletion is assumed and guarded against (for instance, in leukemia Roentgen ray treatment is considered hazardous unless there is a concentration, at least, of 20,000 to 30,000 white cells per cubic millimeter of blood). Few cases of Hodgkin's disease escape Roentgen ray treatment nowadays, so that a leukopenia, when it occurs, may bear a significant relationship to the intensity of Roentgen ray exposure and to the interval of time between treatment. There remains the possibility of a delayed Roentgen ray effect manifesting itself as a leukopenia.*

4. *Bacteriemia.* Since a leukopenia has been noted after a sudden intravenous injection of bacteria (for example, typhoid bacilli) it might be urged that in L. R. a leukopenia followed a sudden blood stream invasion by anhemolytic streptococci. Even if there were incontrovertible proof that bacteria can cause such a leukopenia we would still have to account for the agranular character of this leukopenia in L. R.'s case, and for the absence from his tissues and organs of accumulated granular white cells which might have been swept out of his blood circulation. As a matter of fact, the dissection of this patient's organs, the lungs notably, revealed large clumps of bacteria with no surrounding zone of white cells whatsoever; evidently his tissues failed to respond to the presence of bacteria. Inasmuch as the depletion of his white cells went hand-in-hand with an aggravation of his anemia and with a striking reduction in the number of his platelets, we cannot exclude the probability that his bone marrow and blood-forming tissues suffered a severe general aplasia.

Differential Considerations. The pathogenesis, whatever it may prove to be, of Hodgkin's lymphogranuloma is, perhaps, responsible for the occurrence of a severe leukopenia. Nevertheless, as we have tried to indicate, a variety of causes, alien and unrelated to Hodgkin's disease, may produce a white cell depletion and, obviously, such a leukopenia might be discovered in any patient already afflicted with Hodgkin's disease. There remains, however, a variety of simulating conditions in respect to the leukopenia or to the

* I could not find any carefully controlled observations on this point.

absence of granular cells, and these clinical situations deserve a word of discussion.

Simple lymphocytosis can be produced by severe sepsis or poisoning from extraneous substances like benzol, or by particular infections like pertussis, or by chronic inflammatory processes as tuberculosis, leprosy, syphilis, actinomycosis, blastomycosis, mycosis fungoides, glanders, rhinoscleroma, sporotrichosis. Rarely is the total white count extremely low; moreover some granular cells, however few in number, are found in the blood. It is well to distinguish in this connection a relative from an absolute lymphocytosis. Usually a so-called lymphocytosis is, in reality, a condition wherein the neutrophilic leukocytes are greatly reduced, thereby presenting a secondary but relative increase in the percentage of lymphocytes. This type of relative lymphocytosis accompanies most of the diseases just enumerated. On the other hand, true lymphocytosis, and by this we mean an actual absolute increase in the total number of lymphocytes, is comparatively rare. It does occur in pertussis for instance, the total lymphocytic counts rising to 80,000, or even to 200,000.

Agranulocytic Angina. This term is employed to designate clinically an abrupt overwhelming picture ushered in with fever, chills and severe angina involving the Waldeyer ring (necrosis of the tonsils and the nasal mucous membrane). An occasional case develops insidiously. The condition moves swiftly and is nearly always fatal. Females more than males have thus far been reported, the age incidence ranging from twenty-two to sixty-three years. Striking, indeed, is the blood picture. The granular cells seemingly escape from the blood stream, and there results a relative lymphocytosis and an extreme leukopenia. In this condition no granular cells whatsoever may appear in the blood stream, while the red blood cells and hemoglobin remained practically undisturbed. We have then, unlike the leukopenia seen in Hodgkin's disease, severe throat angina (Vincent's organisms are often present), a quickly overwhelming clinical course associated with no anemia and with no stigmata of Hodgkin's disease. Unfortunately, as already discussed, a severe anemia is frequent in Hodgkin's disease, so that under such circumstances we cannot diagnose with certainty agranulocytic angina because, to begin with, the red blood cells and hemoglobin may not have been spared. Nor is it possible to state, at this time, whether the agranulocytosis and white cell depletion are an effect of a bacteriemia or whether they indicate a peculiar failure on the part of the host to respond to bacterial infection. This point has bearing upon the consideration of agranulocytic angina as an entity *sui generis*.

Infectious mononucleosis was first recognized by Pfeiffer, and probably represents the condition formerly called glandular fever.

Frequently it is associated with Vincent's angina. Patients become acutely ill, developing sore throat, general but superficial adenopathy, enlargement of the spleen and fever. Recovery is usual. The spleen returns to normal. The red cells and hemoglobin stay practically unchanged. There is a relative lymphocytosis, most of the lymphocytes are mature forms, but a number of immature and even abnormal lymphocytic cells are present. The agranular cells run to 70 or 80 per cent, and this preponderance might arouse a suspicion of acute leukemia. No immature granular cells are found and the total white count is at 20,000 to 30,000.

Despite the fact that we have here a preponderance of agranular cells with little change in the red corpuscles or hemoglobin, also a severe angina, this condition is scarcely to be confused with any of the leukopenias described.

Acute Leukemia. Sternberg denies the validity of such a diagnosis, maintaining that the clinical picture which resembles so-called acute leukemia is, in reality and fundamentally, an infection, peculiarly capable of rousing the blood-forming organs and tissues to simulate a clinical syndrome like leukemia. Be this as it may, leukemias with palpable or visible signs of abnormal spleen, liver, nodes, skin, mucous membrane, fundi and so forth, offer small probability for confusion, because the blood is apt to exhibit large numbers of lymphocytic and lymphoblastic cells or myelocytic and myeloblastic cells in various stages of immaturity, together with hemolysis, bleedings, change in platelet count. More especially, one might have to consider the leukopenic types of leukemia, so-called aplastic or subleukemic leukemia. Stated simply, in this type there are clinical manifestations of leukemia, but with a total white count strikingly reduced, so that the blood picture of leukemia is spread before us in a limited and greatly decreased quantity of white cells.

Thrombocytopenia. A possible though remote cause for confusion might exist here for the novice, because in this condition there is a marked reduction in the total platelet count. There are, however, bleedings, an enlarged spleen as a rule, a normal coagulation time, a prolonged bloodclot retraction period and hemolytic phenomena. But there is no leukopenia and no lymphocytosis.

Aplastic Anemia. This term is meant to indicate a depletion or exhaustion of the bone marrow and blood-forming tissues. As a consequence, the sources for blood regeneration and replacement no longer function adequately, and all blood-forming elements—red cells (hemoglobin), leukocytes and platelets are depressed in number. Practically no platelets are seen and the leukopenia is extreme.

It is obvious that since we do not understand the etiology of many of the conditions enumerated above we cannot exclude them

as causative factors in the production of the leukopenia seen in Hodgkin's disease, and this takes on additional force because we do not know how or if the lymphogranuloma process alone produces any of the blood changes observed during the course of Hodgkin's lymphogranuloma.

NOTE.—I am indebted to Dr. Paul Klemperer for the autopsy reports and the photomicrographs.

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HODGKIN'S DISEASE OF THE SKIN AND MUCOUS MEMBRANES.

WITH REPORT OF A CASE WITH UNUSUAL LESIONS.

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IN 1832, Hodgkin first drew attention to the disease which now bears his name, and though recent medical literature fairly teems with reports of clinical, pathologic and bacteriologic studies of this condition, its etiology remains obscure. Proper treatment may seem to retard its onward march, improvement being noted for months, or even a few years, but real cures are questionable.

In spite of classical descriptions of the clinical aspects of Hodgkin's disease, its early diagnosis is not always easy. In the large majority of cases the symptoms are caused by either (a) lesions of the superficial glands, (b) the presence of intrathoracic lymphadenoma, or (c) abdominal lesions.

It is, however, possible, to find Hodgkin's disease revealing its presence by cutaneous manifestations. Kurt Ziegler,^{1,2} from a review of the literature and a study of 70 cases, felt that one-fourth of all cases, at some time or other during their illness, showed evidence of skin involvement. He stated that in from 5 per cent to 12 per cent of the cases the skin symptoms preceded the general ones.

In 1917, H. N. Cole³ studied the records of 29 cases that had been observed over a period of fifteen years at the Lakeside Hospital, Cleveland, in addition to 4 personal cases and 1 seen in consultation. Of these 34, 13 showed more or less cutaneous symptoms and lesions in connection with their generalized condition. As near as can be determined from a perusal of Cole's paper, in only one is there a possibility that the cutaneous symptoms preceded the general ones.

Ziegler has thoroughly described the usual skin lesions. Cole has again enumerated them and added to the original descriptions, giving conclusions based upon his own experience. His article contains several good illustrations. The commonest skin symptom is a pruritus. Next in frequency is a prurigo-like exanthem. Rarely does one encounter a diffuse exfoliating erythrodermia. Urticaria has been seen in many cases and Kreibisch reports a generalized eruption antedating other evidence of the disease by six months. Edematous swellings, permanent or transitory, pigmentations, spotted or diffuse, and disturbances in the nutrition of the skin are also encountered. Reddish or bluish skin tumors have been described. Cole has but 1 such case in his series. Pancoast¹⁰ has recently reported herpes zoster in several cases of Hodgkin's disease. Fox⁴ has described a case of true Hodgkin's disease of the skin and again emphasizes the rarity of such occurrences, reviewing

the literature up to date. Fox states that the histologic differentiation between mycosis fungoides and Hodgkin's disease may be very difficult. In fact, Ziegler in 1910 made the same statement, and after a detailed study of the literature, still wondered whether mycosis fungoides was not but a special form of Hodgkin's disease. It is well known that in lymphatic leukemia, lymphoid infiltrations occur in the skin and subcutaneous tissues, though, according to Butler,⁵ less than one hundred such instances have been recorded. In some of the recorded cases, these infiltrations were the first and only recognizable symptom of leukemia or pseudoleukemia.

Ulcerative lesions of the skin occur only late in the disease and are of no diagnostic importance. Lesions of the mucous membranes are most rare. Ziegler^{1,2} quotes Haeckel as having observed nodules in the mucous membrane of the upper lip, and Dutoit, in the hard palate. Lesions of the mucous membranes are not even mentioned by Desjardins and Ford⁶ in their statistical résumé of cases occurring at the Mayo Clinic for the five year period 1915-1920.

In Kren's¹¹ case, ulceration of the skin occurred. Diagnoses of sarcoma, of syphilis, of tuberculosis, and even of iodism were considered at different times, in spite of negative tissue examinations. Hodgkin's disease was disclosed by the autopsy, which also revealed ulcerations of the mouth, throat, tonsils and gastrointestinal tract.

In 1911, Ziegler² spoke of cases where symptoms indicated early bone involvement, and suspected that other instances had been observed, but not recognized as Hodgkin's disease. A thorough radiologic study of all patients with suspected or proven Hodgkin's disease would probably reveal a larger percentage with early bone lesions. This is well shown by the discussion following the report of a case by Pfahler and O'Boyle⁷ to the Roentgen Ray Society in 1924. Once their attention was drawn to this condition, several members recalled having seen radiograms suggesting similar lesions. For the most part, bone destruction has been noted late in the disease, and I too, have seen such cases.

The blood picture in Hodgkin's disease seldom shows changes sufficiently characteristic to assist in making a diagnosis. Anemia usually occurs sooner or later with, at times, increased platelets. According to some observers, leukocytosis occurs only in the presence of fever or acute infection, counts of 60,000 having been recorded. Leukopenia is often noted. In Ziegler's¹ series, 22 had counts from 5500 to 10,000, 8 from 20,000 to 30,000, 2 over 30,000, and in 18 cases leukopenia from 5500 to 2000. Eosinophiles are often increased; in 15 of Ziegler's cases from 4 to 28 per cent, though on the other hand, they were absent in but 4 cases. The percentage varied, however, at intervals in individual cases. Neutrophils were frequently greatly increased; rarely was the percentage more than slightly decreased, this decrease being accompanied by a relative increase in the large mononuclears. Lymphocytes usually were relatively and often absolutely decreased, very seldom slightly

increased. Ziegler finds but 1 case, Gütig's, a fatal one, where with a very severe anemia and an insufficiency of the bone marrow as in aplastic anemia, the lymphocytes rose from 22 to 50 and then 99 per cent just before death, with a white count of 2000 at the time. The red cells had been about 1,000,000, the hemoglobin 20 per cent. In 18 cases where the blood was especially studied by McAlpin,⁸ no unusual counts are recorded.

The following case is reported because of the unusual lesions of the skin, preceding by many months the other manifestations of the disease. These skin lesions cleared up, but in later stages of the illness, lesions of the mucous membranes appeared, with marked destruction of tissue. At necropsy the appearance of the tissues was so unusual that until a thorough microscopic study had been completed, the pathologist doubted the correctness of the clinical diagnosis. The absence of the usual gland enlargements, the finding of adrenal glands fully the size of lemons, and suggesting tuberculosis, even though other tuberculous lesions were absent, led the pathologist to suggest my giving as cause of death "secondary anemia," contributory, "adrenal tuberculosis." The adrenal involvement had apparently not caused sufficient destruction of tissue to produce any great asthenia or hypotension at a period when this might have been recognized. Ziegler states that clinical evidence of adrenal involvement has not been noted in any case reports. Laporte⁹ observed a patient with asthenia, hypotension and pigmentation of the skin, but concluded upon clinical grounds alone, in the absence of other evidence, that he was not justified in assuming adrenal lesions to explain this so-called Addison's syndrome.

Case Report. *Past History.* Mrs. B. first consulted me August 8, 1914. At that time she gave a history of having been under medical care in 1908 because of "nervousness, crying spells," and also at other times because of hemorrhoids. Before consulting me, she had been treated for several months because of "pain in the left side of neck, shooting pains in the head, general miserable feeling, light-headedness, marked nervousness, irritability, and so forth" and she was "afraid she was going to lose her mind."

I had known Mrs. B. for several years. She was a good natured, usually jolly woman, with no special worries to account for her neurosis. Though only 5 feet 6 inches tall, she weighed 192 pounds, had a rather large jaw and fairly well-separated teeth, suggesting old pituitary disease. The only signs of importance were a systolic blood pressure of 160, an aortic systolic murmur, prominent abdomen, and a slight trace of albumin in the urine.

Chloral and bromides, hydrotherapy, and proper diet brought about a general improvement with a loss of 16 pounds in one month. Nervous symptoms recurred at times, but six months later, systolic blood pressure was down to 120. In 1916, very large, irreducible hemorrhoids of 20 years' standing gave considerable trouble follow-

ing the drinking of laxative waters, eating of spicy foods, and so forth. An ointment was prescribed, containing adrenalin, cocain, belladonna and tannic acid. This was used for several years, whenever indicated, that is, especially during February, 1919, when the hemorrhoids formed a mass the size of a fist, with several areas denuded of mucous membrane. Operation was consistently refused.

In March, 1917, Mrs. B. had an acute laryngitis and slight bronchitis, in August, 1918, a slight febrile throat infection. In August, 1921, she was again nervous; the menstrual periods came at intervals of 23 to 24 instead of 26 to 28 days. Her weight was 205 pounds; blood pressure, 200 systolic, 110 diastolic. The urine was normal; the phthalein excretion was 59 per cent in the two-hour period after intramuscular injection. Corpus luteum was prescribed and the diet again regulated.

On July 6, 1923, that is, after an interval of one and a half years, Mrs. B. was asked to report for examination. Her weight was 193 pounds; blood pressure, 180 systolic, 100 diastolic; pulse rate rapid, due to nervousness. The urine was entirely negative. A complete blood count was normal.

Present Illness. On March 20, 1924, Mrs. B. reported that a week before, spots had appeared at various parts of her body. She had thought they were hives, but they did not itch. Examination showed the following: Weight 187 pounds. Of the lesions referred to, 2 were seen on the back, each the size of a nickel, raised, firm, rounded, nodular. They were of the same color as the surrounding skin, possibly a little whiter in the center. A third spot was on the right side of the neck, only much smaller than the others. The urine was normal; blood: hemoglobin 85 per cent, differential normal.

March 27, 1924. Weight 183½ pounds. One new spot was noted at the angle of the jaw. A complete examination, including blood tests, revealed no other changes. The duration of the skin lesions and the absence of itching eliminated the possibility of urticaria. A drug etiology did not seem likely, as the only ones that had been used were in the ointment (presented in 1916.) The Wassermann reaction was negative. Dr. Howard Morrow was consulted. He considered the skin lesions "a curiosity," but advised repeating the blood tests in view of a possible change to a leukemic blood picture.

April 9, 1924. For over a week, she had had occasional pain in the right elbow. Nothing was found to account for this. There were no palpable glands. The skin lesions on the back had not changed. There was a new spot, the size of a nickel, on the bridge of the nose. In spite of the full, fat abdomen, the spleen edge was just palpable at the costal margin, smooth and regular. The liver was not palpable. The urine was negative.

April 14, 1924. She felt warm and "achy." Examination: Temperature, 102.8°. Pulse, 120. Nose, throat, sinuses and lungs were apparently negative. The heart was as usual. The spleen edge was palpable. The spots were larger and more prominent.

The one on the nose was extending toward the eye; those on the back had coalesced.

Dr. Morrow still thought the lesions might be due to an early leukemia, but that mycosis fungoides had to be considered. Rolleston states that in mycosis fungoides the lymphatic glands are almost always enlarged, and the cutaneous tumors much larger than those seen in Hodgkin's disease.

In spite of medication, the patient's temperature had remained around 102 for a few days, and new skin lesions had appeared, but after nine days, fever had disappeared. Excision of a nodule had not been permitted.

May 7, 1924. Weight 174 pounds. On the anterior surface of the body, there were 4 fading lesions; on the back, 12; 1 on leg. They were flat and barely visible. The abdomen was firm. The spleen was at the costal margin. The liver was 2 inches below the costal margin. Iron and arsenic were prescribed.

May 26, 1924. She had been fine for several weeks, but on the 25th her temperature had suddenly gone to 104°. Mrs. B. looked very ill, but all skin manifestations had entirely cleared up. The lips had felt swollen and numb, but no cause for these sensations had been found.

June 5, 1924. Mrs. B. was well enough to come to the office. A thorough physical examination, including pelvis and nervous system, added nothing connected with this illness. Her complexion was pale and pasty. The spleen edge was 2 inches below the costal margin, soft and sharp. The hemorrhoidal mass was as usual, not bleeding and not infected. The blood picture was remarkable. There were no polymorphonuclear neutrophils. There were 89 per cent lymphocytes, and 9 per cent abnormal cells, apparently myeloblasts. Myeloblasts were not seen in any previous or subsequent examinations. Fluoroscopic examination showed lung fields to be clear and there was no evidence of masses in either hilum. Posterior mediastinum was clear. Radiograms of teeth were negative.

October 25, 1924. Mrs. B. had progressed nicely for over four months and then had begun to look poorly again, temperature had risen on October 21, reaching 101°-103° at night. After that she developed a swelling and edema of the right eyelid with a definite area of infection. There were harsh breath sounds with prolonged harsh expiration over the right upper posterior part of chest. She had a dry, hacking, not paroxysmal cough. The abdomen was most of the time greatly distended and tympanitic, but at times the spleen could be felt on a level with the navel. The liver dullness seemed a bit high; the lower edge came down below the rib borders. There was a systolic murmur over the entire precordium, but the cardiac murmurs were of such long standing that an endocarditis did not seem likely. A study of the literature (here presented) had made me feel that I should have considered Hodgkin's disease as a possibility long before this date.

November 12, 1924. During the last week, lesions had appeared on the hard palate. They had broken down, ulcerated, and one of them looked like a punched out ulcer, suggestive of a luetic gumma. There was also a sloughing lesion on the opposite side, and a sloughing lesion had occurred in one of the hemorrhoids. Smears had shown organisms considered as secondary invaders. Local medication had failed to check the progress of these lesions.

November 14, 1924. Fluoroscopic examination, to my surprise, still showed no chest abnormalities, that is, glandular enlargements, such as could be expected with Hodgkin's disease. Fever had persisted. Iron and arsenic had been continued and Roentgen ray treatments instituted, the mouth lesions being exposed at weekly intervals. Some local and general improvement had followed.

December 5, 1924. Mrs. B. had now developed a diffuse eruption over the extremities, trunk and back. In some places there were areas suggesting urticarial lesions; in others the patches were elevated, white in color, and of various sizes. Pruritus was intense and resisted the remedies usual in such cases. I did not feel that the eruption had been caused by the arsenic, but believed it a part of the disease. A consultant who had seen the patient on several previous occasions and who had shared my doubts, on this date had thought an aleukemic leukemia could not be excluded, because of the mucous membrane involvement.

Mrs. B. grew gradually weaker. After ten Roentgen ray treatments, they were discontinued. The slough on the left side of the hard palate had finally come off, exposing a perforation, and thereafter fluids had often come out through the nose. A general but rapid decline had followed, and Mrs. B. died December 28, 1924, nine months after the first appearance of skin lesions.

Date.	Hemoglobin per cent.	Red blood cells in millions per c.mm.	White blood cells in thousands.	Polymorphonuclears.	Large mononuclears.	Small lymphocytes.	Eosinophils.	Mycoblasts.	Basophils.	Transitionals.	
July 6, 1923	77	4.46	11.2	73	3	24	0	0	0	0	Reds: marked pallor. Slight anisocytosis.
Mar. 20, 1924	85	72	4	23	0	0	0	1	
Mar. 27, 1924	8.4	4	23	0	0	0	3	
April 2, 1924	80	10.2	68	22	6	0	0	1	3	
May 7, 1924	64	3.65	6.0	63	5	26	1	0	1	1	
May 21, 1924	70	3.6	7.0	64	5	27	0	0	1	4	
May 27, 1924	70	3.75	6.2	49	14	33	0	0	0	4	
June 5, 1924	60	3.15	5.4	0	2	89	0	9	0	0	
Aug. 13, 1924	78	4.09	8.2	67	3	26	0	0	0	4	
Aug. 20, 1924	80	4.12	8.6	66	4	27	1	0	0	2	
Sept. 4, 1924	69	3.55	6.2	65	5	26	1	0	0	3	
Oct. 1, 1924	76	3.9	6.0	66	4	28	0	0	0	2	
Oct. 15, 1924	78	4.1	6.2	66	5	23	2	0	0	4	
Oct. 21, 1924	70	3.7	5.0	65	4	27	1	0	0	3	
Nov. 12, 1924	45	2.27	2.0	37	2	57	0	0	0	4	
Nov. 25, 1924	55	2.79	3.0	65	3	31	0	0	0	1	
Dec. 23, 1924	40	2.26	2.4	63	4	32	0	0	0	1	

Necropsy performed ten hours later by Dr. G. Y. Rusk.

ANATOMICAL DIAGNOSIS. Hodgkin's disease of spleen with extensive infiltration in liver, kidneys, both adrenals, where the process is associated with extensive necrosis. Infiltration and necrosis of lymph node near head of pancreas. Marked myeloid hyperplasia of bone marrow with lymphocytic infiltration and occurrence of cells of the "Reed" type. Ulceration and perforation of the hard palate with reaction suggesting Hodgkin's type. Superficial infiltration of epicardium. Slight chronic fibrosis of myocardium. Slight interstitial pancreatitis. Aortic atheroma. Moderate obesity.

Of especial interest were the absence of palpable superficial lymph nodes, the irregular perforation, averaging 2 cm. in diameter, in the left side of the palate; and the adrenal masses. The left kidney was normal in size; the adrenal was adherent to it. On section through the kidney and adrenal, there was a large, opaque, white, necrotic area principally occupying the adrenal, but also extending into the kidney. About this area there was an area of hyperemia. Little normal adrenal tissue was to be seen. The right adrenal was also largely occupied by a similar necrotic mass which, however, did not invade the kidney tissue as that on the left. The necrotic mass on the left measured about 5 x 3 x 3 cm., that on the right, including the adrenal, measured 5 x 6 x 3 cm. It is unfortunate that circumstances never permitted microscopic examination of the skin lesions.

Gross Description. Remains of a stout female adult appearing about fifty years of age. Superficially examined, shows skin entirely negative, and no palpable superficial lymph nodes. The left side of the hard palate shows a perforation irregular in outline averaging about 2 cm. in diameter. Hemorrhoids are present. The extremities appear negative. On making the usual median incision the body fat is abundant. The voluntary muscles appear normal. The peritoneal cavity shows no fluid and no adhesions are present except as described below. The pleural cavities appear normal. The pericardial cavity contains about 250 cc. of clear straw-colored fluid.

Heart appears slightly enlarged, especially to the right. The epicardial fat is well marked. The muscle is soft and somewhat flabby. There are a few small petechiæ on the epicardium. The right auricle is full; internally appears normal. The wall of the right ventricle shows well-marked fatty infiltration. It measures about 5 mm. thick. The left auricle is negative. The mitral orifice measures 10 cm. The valve appears normal except for moderate atheroma at its base. The aortic orifice measures 8 cm. The atheroma from the mitral valve is coextensive with that along the bases of the aortic cusps. The cusps are otherwise negative. The tricuspid orifice measures 10 cm., the valve appears normal. The

pulmonary orifice measures 8 cm., the cusps appear normal. The wall of the left ventricle measures 11 mm. The endocardium shows a few yellowish spots due to fatty alteration. The myocardium is soft, somewhat pale brownish cast, and slightly mottled as if due to fatty alteration.

The first portion of the aorta shows well-marked atheroma which extends into, and surrounds the coronary orifices.

The right lung weighs 425 grams. The pleural surface shows the usual anthracosis, but otherwise appears quite normal throughout. There is an accessory upper lobe about 4 x 6 x 2 cm. On section the middle lobe shows a slight edema. The lower lobe is markedly edematous. The larger bronchi show a slight hyperemia of the mucous membrane, but no exudate is seen. The nodes at the root of the lung show well-marked anthracosis.

The left lung weighs 340 grams. It is similar to the other lung throughout, except for moderate edema at the base.

The spleen weighs 760 grams. It measures 21 cm. in length by 9 cm. broad by 8 cm. thick. Superficially it appears coarsely mottled; areas of a deep reddish-brown intermingled with areas which appear distinctly paler. This differentiation of color extends into the tissue on section. The surface of the spleen is free from adhesions. Its anterior border is lobulated. On section, in addition to the variations in color, the tissue appears moderately firm; the Malpighian bodies cannot be definitely distinguished. The tissues do not collapse; the cut vessels appear negative. No evidence of thrombosis is seen.

Liver weighs 2060 grams. It is somewhat pale, yellowish-red in color. There is a small cyst about 3 mm. in diameter on the superior surface of the left lobe. On section the liver is irregularly dotted with many small pale yellowish areas scattered throughout the liver. There is no evidence of cirrhosis. On the under surface of the liver at the site where the adrenal lies adjacent to it, there is an area of necrosis coextensive with, and adherent to a similar necrotic mass in the adrenal as described below.

Adrenals. The left kidney is normal in size. The adrenal is adherent to it. On section through the kidney and adrenal there is a large necrotic area, firm, opaque and white, principally occupying the adrenal, but also extending into the kidney. About the necrotic area there is an area of hyperemia. Little normal adrenal tissue is to be seen. This necrotic mass is less bound to the surrounding tissues than might be expected. The right adrenal is also largely occupied by a similar necrotic mass which, however, does not invade the kidney tissue as that on the left. The necrotic mass on the left measures about 5 x 3 x 3 cm., that on the right including the adrenal measures 5 x 6 x 3 cm.

Kidneys. The kidneys are of normal size. The left is encroached upon by the granulomatous mass as noted in the previous paragraph.

About this region there is some blurring of cortex. The cortex in general is of normal thickness; somewhat pale, markings rather indistinct. No gross evidence of fibrosis. Medullary substance appears negative. The pelves are negative.

At the head of the pancreas there is an enlarged lymph node measuring about 2 x 1 x 1 cm. On section, this also shows a large firm opaque white necrotic center similar to that of the adrenal picture. A few other enlarged glands are seen in this region. The pancreas proper appears to be of normal size. It is slightly increased in density, especially toward the distal portion; appears otherwise negative.

The mesenteric lymph nodes appear normal. Those in the retroperitoneal region are generally moderately enlarged, but show no evidence of necrosis. The mucosa of the gastrointestinal tract is negative throughout.

The uterus, bladder, tubes and ovaries appear normal.

Central nervous system not examined.

Microscopic Examination. Microscopic examination of heart and epicardium shows superficially a slight infiltration with lymphocytes, a few plasma cells and undifferentiated mononuclear cells. In the myocardium there are a few foci of chronic fibrous tissue replacement of the myocardium. Lungs are negative. Stomach and the remainder of the gastrointestinal tract negative.

The mouth lesion shows normal epithelium. The subepithelial connective tissue shows an extremely extensive infiltration with lymphocytes, huge numbers of plasma cells, scattered eosinophiles and occasionally a multinucleated cell with deeply staining, compactly arranged nuclei and basophilic cytoplasm.

The spleen shows some areas of marked hyperemia and other areas in which the tissues appear much more cellular. The Malpighian bodies are small. The pulp elements generally are suffused with mononuclear cells of undifferentiated type, occasional plasma cells, and scattered large mononuclear cells with clearly staining nuclei and abundant cytoplasm, and also occasionally small polynuclear cells, at times showing a cluster of clear nuclei with relatively abundant eosinophilic cytoplasm and in other instances the nuclei more compact, more deeply staining, and the protoplasm more basic. Rarely in this group of cells a mitotic figure is seen. Among the large mononuclear cells some are seen with lobulated nuclei.

Sections of liver taken through the area adjacent to the right adrenal shows an area of necrosis surrounded by an illy-defined layer containing bloodvessels apparently in part derived from the preëxisting liver vessels. This layer also contains irregular accumulations of lymphocytes, plasma cells, some fibroblastic elements, and a number of undifferentiated mononuclear cells, but no cells which are typical of the Hodgkin's process.

Sections taken from other portions of the liver, as well as adjacent to the necrotic area show almost universally an infiltration of the portal spaces by lymphocytes and plasma cells and a varying number of large mononuclear cells with varying amounts of cytoplasm.

Sections from the left kidney show a process in the region adjacent to the necrotic adrenal analogous to that seen in the corresponding portion of the liver. The kidney sections in general also show extensive, although irregular, infiltration with lymphocytes, plasma cells and undifferentiated mononuclears analogous to that seen in the liver. The kidney parenchyma shows cloudy swelling, especially the convoluted tubules.

Sections from the adrenals show extensive necrosis, the necrotic tissue being irregularly outlined by similar reactive type of cell which extends to irregular distances in between the adrenal tissue proper. Here the infiltration often takes on a perivascular arrangement. In this region occasional polynucleated cells of the type seen in the spleen are encountered.

Sections from the pancreas show a slight interstitial fibrosis which very rarely shows an infiltration with a few scattered lymphocytes and plasma cells. The islands are irregular in size, some of them reaching relatively large volumes. They do not, however, show any abnormality.

Sections from the ovaries are negative.

Mediastinal lymph nodes show marked pigmentation. The tissues are more or less dissected apart as if by edema. The lymphocytic elements are relatively inconspicuous while the endothelial are abundant. The mesenteric and retroperitoneal lymph nodes also appear edematous and contain an irregular infiltration with mononuclear cells of the endothelial type.

Sections of the special node lying near the head of the pancreas which show necrosis in the gross, shows microscopically extensive necrosis occupying practically the whole of the gland except for a superficial area where the tissues are markedly edematous, show a layer of fibrin and beyond this scattered lymphocytes, plasma cells and mononuclear cells of medium size.

Sections from the aorta show a well-marked atheroma.

Femoral bone marrow appears markedly cellular. There are small focal groups of erythroblastic elements and numerous myelocytes which predominate the picture. Most of these are apparently of the neutrophilic type, the eosinophiles being relatively infrequent. Scattered among the myelocytes are a moderate number of lymphocytes. There also occur scattered cells with large oval and single, or lobulated nuclei; the nuclei sometimes stain palely and there is abundant and moderately eosinophilic cytoplasm. These cells, while infrequent, suggest the "Reed" type of cell.

Conclusions. 1. The early diagnosis of Hodgkin's disease is not always easy.

2. Cutaneous manifestations may give the first warning of the onset of this fatal disease.

3. They may precede all other symptoms or signs by several months, and as in the present case may disappear, recur, and disappear again.

4. Lesions of the mucous membranes and of the bones are by no means so rare as the older literature would indicate.

5. A differential diagnosis cannot always be made upon purely clinical grounds, even late in the disease.

6. Very sudden changes may occur in the blood picture. Frequent examinations are necessary so as not to overlook them.

7. Considerable adrenal involvement may occur without producing symptoms leading to its recognition.

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RENAL GLYCOSURIA AND PENTOSURIA.

A DISCUSSION OF THE SIMILARITY OF THE TWO CONDITIONS.

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THE terms "renal diabetes" and "renal glycosuria" are given to a condition which is characterized by the presence of dextrose in the urine more or less continuously; by a normal blood sugar content; by the absence of the usual symptoms of diabetes; by the fact that the condition does not become true diabetes; that it sometimes

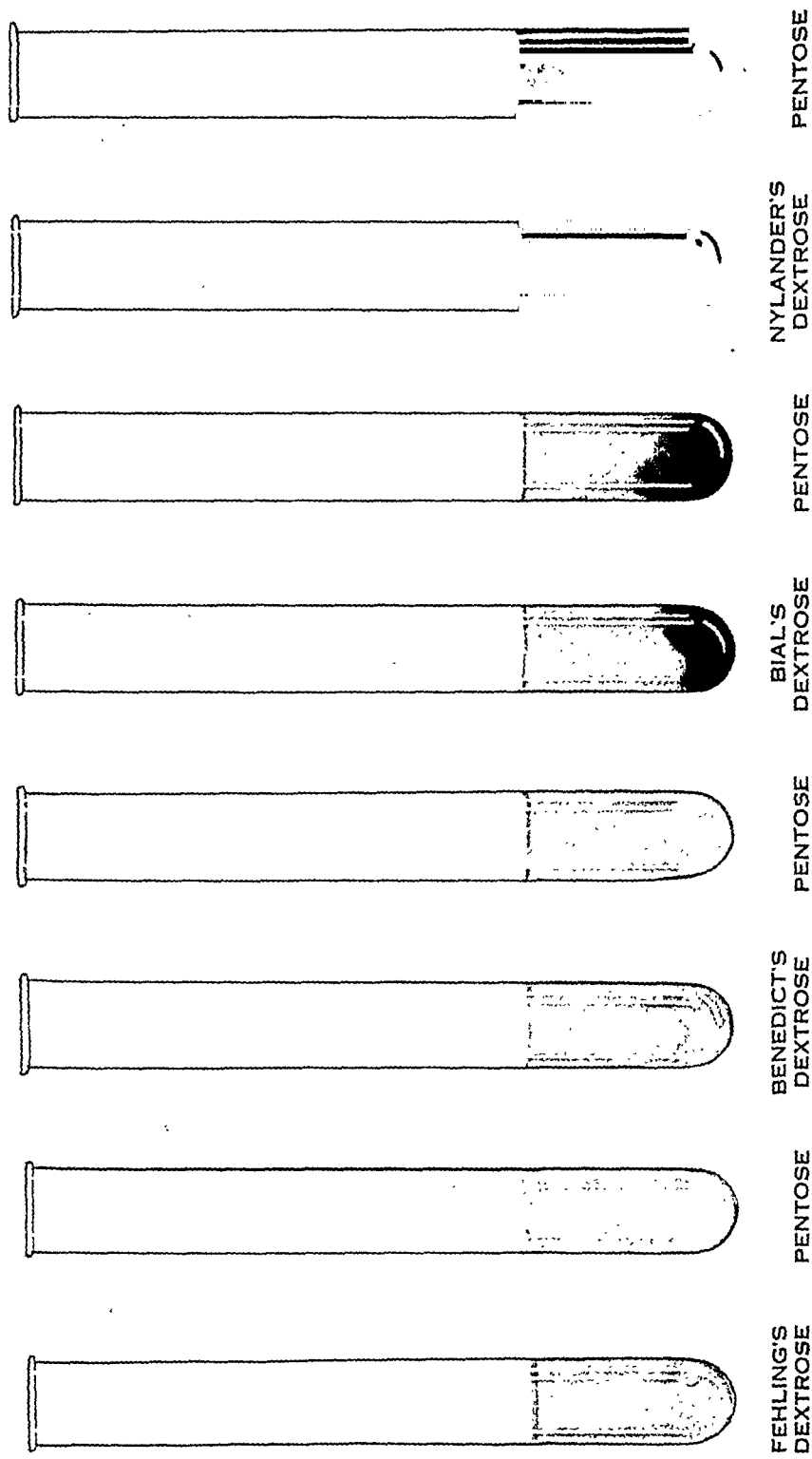
occurs in more than one member of a family; that the usual tests for renal function yield normal results; that the urine does not indicate the presence of nephritis and that the pancreatic function is not disturbed. Although the etiology is unknown, it is suggested that a congenital renal defect exists which permits sugar to be present in the urine in amounts detectable by the usual laboratory tests. Renal glycosuria is a better term for this condition than renal diabetes.

Renal Glycosuria and Diabetes Mellitus. Many cases have been reported in the literature since 1896, and the importance of the differential diagnosis between true diabetes and renal glycosuria has been emphasized. In differentiating renal glycosuria from diabetes mellitus a consideration of the following points is important: The absence of the symptoms of true diabetes; the normal blood sugar; the normal reaction of blood sugar to the ingestion of glucose and the presence of a normal respiratory quotient after carbohydrate ingestion.³

Essential Pentosuria. Essential pentosuria is a condition occurring most commonly in the Jewish race. It is often present in several members of the same family. It is characterized by the presence of a pentose in the urine more or less continuously; by the presence of a normal blood sugar; by the absence of evidence of deficient renal function or other signs of nephritis; by the absence of symptoms of diabetes; by the fact that a high carbohydrate intake does not increase the pentose; that the pancreatic function is normal and that the condition never becomes diabetes to the exclusion of pentosuria. Although there are less than 100 cases in the literature, pentosuria occurs more frequently than is suspected, and often goes unrecognized. Stokey,¹⁰ in a study of routine urines, found 15 in which pentose was present. Janeway³ stated that the condition was probably an anomaly of the intermediate metabolism and analogous rather to cystinuria and alkaptonuria than to diabetes. Characteristic symptoms are absent, although signs of unstable vasomotor control, gastrointestinal disorders and neurasthenia have been observed in many of the patients.

The similarity between pentosuria and renal glycosuria is marked. The cause is unknown. Neither present symptoms of diabetes. The blood sugar is normal. The glucose tolerance test yields similar results. The condition may be present in more than one member of a family. The renal function tests yield normal results and the urinary reducing substance reacts with Fehling's, Nylander's and Benedict's tests in such a manner that it is impossible to differentiate by this means.^{5,7}

Differential Diagnosis. The fermentation test is considered by many to be the best test to differentiate dextrose from substances which reduce the chemical test solutions, but Voit⁶ has shown that under certain conditions a small quantity of L arabinose added to a urine from a diabetic may be fermented with the dextrose, and



The Similarity of the Reaction of Dextrose and Pentose in the Usual Reduction Test Solutions.

Castellani,³ in a recent article, has emphasized the fallacies of the ordinary fermentation test. (2) Bials'¹ modification of the orcein test yields a greenish precipitate and a greenish supernatant fluid with pentose. The reagent is prepared as follows: One gram of orcin is dissolved in 500 cc. of hydrochloric acid of a specific gravity of 1.151. To this add 25 drops of a 10 per cent solution of ferric chloride. Keep in an amber colored bottle. Garrod states that with this reagent a clear cut differentiation from dextrose may be obtained, but we have found that dextrose will sometimes give a precipitate very much like that of pentose. (3) The urine of most pentosurics is optically inactive, but a few apparently yield a dextrorotary osazone.⁵ (4) With the phenylhydrazin test a crystalline osazone is obtained which, however, is rather difficult to differentiate from glucosazone. (5) The melting point of crystals after recrystallization serves as one of the most certain methods of differentiation.⁴ The melting point of the glucosazone is 205° C. and that of the pentosazone 156° to 160° C. The theoretical nitrogen content of pentosazone is 17.07 per cent. This estimation insures complete certainty of the nature of the crystal. (6) A. Neuman⁹ devised a modification of the orcein test which produces distinctive colors and spectra with pentose and dextrose. (7) Castellani and Taylor² were able to diagnose a case of pentosuria, using the specific bacteria by which that substance in the urine may be fermented.

Because of the similarity between these two conditions clinically, and because of the similarity of the reduction with the usual tests for urinary sugar, we investigated 52 reports on this condition found in various journals during the past seven years, with a view to determining how the diagnosis of dextrosuria was made, and whether the diagnosis of pentosuria was considered. If desired, the list of articles and tests may be obtained from the authors.

In the articles reviewed we have counted fifty tests used, but failed to find mention of the determination of the melting point of the osazone crystals or of the estimation of nitrogen content, or the Bial chemical test for pentose. The phenylhydrazin and the fermentation tests were performed in only a few instances.

Discussion. It is not our intended purpose to discredit in any way the work that has been done, but to emphasize the importance of more careful differentiation, first between dextrose and other sugars and secondly between dextrose and pentose. Renal glycosuria and essential pentosuria have much in common clinically. Differentiation with the ordinary reduction tests is impossible. In view of the results of this investigation, it may be assumed that some of the cases reported as renal glycosuria may have been essential pentosuria. We recommend; therefore, that in order to differentiate between renal dextrosuria and diabetic dextrosuria, the following tests be used: (1) The fermentation test following the suggestion of Castellani and Taylor; (2) the estimation of the respi-

ratory quotient in the determination of carbohydrate utilization; (3) the blood sugar tolerance test.

To differentiate between dextrose and pentose, the following tests should be used: (1) The Bial test, being careful to follow the technique herein described as recommended by Bial; (2) the phenylhydrazin test for dextrosazone and pentosazone crystals; (3) after recrystallization determine the melting point of the crystals; (4) the determination of the nitrogen content of the crystals; (5) the spectrum test of Neuman.

Renal diabetes might well be classed as one of the inborn errors of metabolism together with pentosuria, alkaptonuria, cystinuria and hematuria congenita.

Summary. Renal glycosuria and essential pentosuria, clinically, present similar features.

Pentose and dextrose cannot be differentiated by the use of the usual reduction tests, Fehling's, Benedict's or Nylander's.

The bakers' yeast fermentation test may fail to differentiate these two substances.

Bial's test is useful, but not always accurate in the differentiation.

The differential diagnosis is made by Bial's test; by the special fermentation method of Castellani and Taylor; by the estimation of the melting point of crystals, using the phenylhydrazin test; by Neuman's spectroscopic method and by the estimation of the nitrogen content of the crystals.

The differential diagnosis between renal glycosuria and diabetes mellitus is made by the blood sugar estimation; by the blood sugar tolerance test; by the estimation of the respiratory quotient after carbohydrate ingestion.

From a survey of the literature of renal glycosuria it is noted that the phenylhydrazin and fermentation tests were performed in only a few instances, also that Bial's test, the determination of the melting point of crystals, the estimation of the nitrogen content of crystals and the special fermentation test were not used.

The possibility that some of these reported cases may have been pentosuria is suggested.

The necessity of a more careful differentiation is emphasized.

Renal diabetes might be included in the group of conditions designated as "inborn errors of metabolism," pentosuria, cystinuria, alkaptonuria and hematuria congenita.

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PERITONEAL ABSORPTION: COMPARISON BETWEEN THE NORMAL AND THE INFLAMED PERITONEUM.*

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Introduction. The possible difference that might exist between the rate of absorption in the normal peritoneum and that in the inflamed peritoneum was investigated with the hope that data might be obtained which would be of value in the treatment and care of clinical peritonitis.

The literature on peritonitis and peritoneal absorption is so voluminous that only a brief review will be attempted here. Carson has sketched the history of peritonitis, and Klein and McGuire have compiled bibliographies on the experimental work of more recent years in this field. Attention is called to certain historical facts as given by Carson.

In the Fourteenth Century a condition strikingly similar in its characteristics to peritonitis and known as the "iliac passion" was described. In the Seventeenth Century Thomas Willis described puerperal fever, and in the Eighteenth Century Heister reported the first case of abscess of the appendix. A great deal of attention was given to puerperal fever in the Nineteenth Century, and John Hunter pointed out that males were sometimes affected with a similar syndrome. Bichat and Laennec insisted that peritonitis was an entity. Then came the work of Pasteur and Lister, which marked the beginning of a scientific conception of the cause of peritonitis. In 1867 Koeberle, an Alsatian surgeon, first described peritonitis following abdominal operations. Vast strides were made in bacteriology in the latter part of the Nineteenth Century and for the first time peritonitis began to be studied experimentally in animals.

Certain investigations have been of particular importance in determining present conceptions of the mechanism of peritoneal absorption and peritonitis. Buxton and Torrey, Cunningham, Durham, Dutrey, Thiele and Embleton and others reported the absorption of solid particles from the peritoneal cavity into the omentum. Buxton and Torrey, Cunningham, Durham, MacCallum, Muscatello and others found absorption from the peritoneal cavity through the lymphatics of the diaphragm into the anterior mediastinal lymph nodes. Costain, Thiele and Embleton and others reported absorption from the peritoneum into the thoracic duct. Bolton, Clark, Dandy and Rowntree, Hamburger, Orlow, Putnam, Starling and Tubby, and others found that materials were absorbed

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from the peritoneal cavity directly into the blood stream through the subperitoneal capillaries.

Starling and Tubby found that dyes injected intraperitoneally appeared in the blood before the lymph of the thoracic duct was colored. Dandy and Rowntree found phenolsulphonephthalein in the urine of animals in four to six minutes after intraperitoneal injection. Oppenheimer found that toxins injected intraperitoneally appeared in the urine within fifteen minutes and that the time was not changed by tying the thoracic duct. Orlow found that after sodium chlorid solution had been injected intraperitoneally there was no increase in lymph flow from the thoracic duct. Hamburger demonstrated that there was no impairment of peritoneal absorption after ligation of the thoracic duct, and Fisher, that solution injected intraperitoneally exhibited absorption rates similar to those of the lyotropic series when absorbed by unsaturated colloids. Dandy and Rowntree, in comparing the rates of absorption of dye from the peritoneum of animals in various postures, concluded that with the pelvis in a dependent position there was 15 per cent less absorption than in other postures. Costain, believing that the important route of absorption from the peritoneal cavity was through the thoracic duct, made a thoracic duct fistula for the treatment of peritonitis. McGuire and Cox and Bell, however, in repeating this experiment with a larger series of animals, failed to find lymphaticostomy of value in reducing the mortality rate in experimental peritonitis.

Handley has recently suggested that the severe toxemia of peritonitis is due not so much to material absorbed from the peritoneum as to poisons absorbed from the interior of the gastrointestinal tract, in which there is almost complete stasis as a result of paralytic ileus.

The preponderance of evidence in the literature seems to indicate certain conceptions of peritoneal absorption as being adequately substantiated and generally accepted. Fluids and fluid solutions seem to be absorbed chiefly by the subperitoneal capillaries directly into the blood stream. Suspensions and particles, such as lamp black and bacteria, seem to be absorbed chiefly by the lymphatic system, especially those channels leading to the anterior mediastinal and sternal lymph nodes.

Method of Experimentation. Male rabbits weighing about 2 kg. each and female dogs weighing about 10 kg. were selected because of the ease with which they may be catheterized. Animals were gently restrained in the dorsal posture on suitable tables for observation. For all operative procedures ether anesthesia and aseptic technique were employed.

Several dye solutions were tried, but phenolsulphonephthalein was used as a routine because it can be easily and accurately detected in the urine following its injection intravenously and intraperitoneally. One cubic centimeter of the standard solution (0.6 gm.

dye for 1 cc. of solution) was used for all injections. From 10 to 15 cc. of sterile water was added to the routine intraperitoneal injections in order to promote diffusion of the dye to all peritoneal surfaces.

Animals were catheterized with small, soft, rubber catheters, the bladder washed out and a few cubic centimeters of sterile water left in the bladder with the catheter clamped off. This water was withdrawn and returned to the bladder with a syringe at intervals of one minute. Each time a few drops were tested in alkali for the appearance of the dye. In this way very small traces could be readily detected by inspection.

All animals were used first for control experiments. The dye was injected intraperitoneally and the time between its injection and subsequent detection in the urine recorded. This was verified usually two or more times with each animal. In the first experiments all animals, both before and after production of peritonitis, were given both intravenous and intraperitoneal injections of the dye, but the speed of excretion of dye was found so constant in all cases following intravenous injection that its use was discontinued.

After the control experiments had been completed some of the animals were used for studying the rate of absorption and elimination of the dye, in the presence of bacterial peritonitis. This was induced by injecting bacterial cultures into the peritoneum or by directly infecting it at laparotomy. In several of the dogs ordinary operations, such as gastroenterostomy, were performed and the peritoneum soiled with the intestinal contents, in order to simulate conditions giving rise to peritonitis in the human subject. In others mechanical peritonitis was caused either by intraperitoneal injection of irritants, such as aleuronot and iodized starch, or by massaging the visceral and parietal peritoneum with dry gauze sponges at operation. After peritonitis had developed the animals were given intraperitoneal injections of the dye daily as described. The presence and course of the peritonitis were followed in surviving animals at intervals of three or four days by exploratory laparotomy, and finally the condition of the peritoneum at necropsy was carefully noted.

Results. In several rabbits the dye was injected intravenously both before and after the onset of peritonitis. The time from the injection to the detection in the urine was between four and five minutes in every case.

In two series of rabbits various quantities of sterile water, 15 cc., 30 cc. and so forth, up to 150 cc., were injected intraperitoneally. With the injection of 15 cc. of water it was found that the time between injection and detection of dye in the urine was slightly shortened. Large amounts lengthened the time, the greatest lengthening occurring with 105 cc., above which the time gradually decreased. By washing out the bladders of several rabbits at

various intervals following intraperitoneal injection of dye it was found that all the dye was excreted in from six to eight hours.

The dye was injected intraperitoneally in one group of rabbits in various postures. *The time of absorption and detection in the urine was not appreciably altered in any of the experiments.*

In another group of experiments 50 cc. of a hypertonic (50 per cent) sucrose solution was injected intraperitoneally with the 1 cc. of dye. In spite of the fact that such a solution takes up fluid from the peritoneum and almost doubles its volume within an hour, it failed in these experiments to alter the time of appearance of the dye in the urine.

There were 36 experiments on absorption of the dye from the peritoneum of normal rabbits. Conditions were standard, as described, and all observations were made by me. The average time between the intraperitoneal injection of the dye and its detection in the urine was eleven and five-tenths minutes. The mean variation from this average was one and nine-tenths minutes, the greatest variation four and five-tenths minutes.

There were 13 experiments on dye absorption in rabbits with mechanical peritonitis. Conditions were standard, as in the group of normal animals, and the presence of mechanical peritonitis was verified by exploration or necropsy. The dye was injected at intervals from one hour to nine days after the production of peritonitis. The average time of detection of the dye in the urine was eleven and three-tenths minutes. The mean variation from this average was one and six-tenths minutes, the greatest variation three and seven-tenths minutes.

There were 23 experiments on dye absorption in rabbits with bacterial peritonitis. Conditions were standard as in the preceding two groups, and the presence of bacterial peritonitis was verified by exploration or necropsy. Injections were made at intervals of from three hours to seven days after the production of peritonitis. In 18 of the experiments the rates of absorption of dye were fairly constant, and in these the average time of detection of dye in the urine was eleven and eight-tenths minutes. The mean variation from this average was one and nine-tenths minutes, and the greatest variation four and eight-tenths minutes. In the other 5 experiments the absorption times were twenty-nine, thirty-six, eighteen, nineteen, and eighteen minutes respectively. In these 5 experiments adhesive peritonitis was present and the area of peritoneal surface available for absorption was greatly diminished.

In order to provide further data on absorption from the normal and infected peritoneum a series of dogs was used. There were 11 experiments on absorption from the normal peritoneum; in these conditions were standard. The average time between intraperitoneal injection of the dye and its detection in the urine was nine and six-tenths minutes. The mean variation from this average was

one and three-tenths minutes, and the greatest variation two and six-tenths minutes. There were 50 experiments on peritoneal absorption in dogs with bacterial peritonitis. Conditions were standard, and the presence of bacterial peritonitis was verified by exploration and necropsy. Injections were made at intervals of from one to fourteen days after the production of peritonitis. The average time of detection of dye in the urine was nine and three-tenths minutes. The mean variation from this average was one and seven-tenths minutes, and the greatest variation four and five-tenths minutes. In the experiments in which the absorption time was longer than the average adhesive peritonitis was present and the area of peritoneal surface available for absorption was greatly diminished.

Experiments on dogs were more satisfactory than those with rabbits. A typical example of the usual experiment is shown in the tabulation:

PROCEDURES AND FINDINGS IN A TYPICAL EXPERIMENT.

1925.	Procedure.	Interval before recovery of dye (min.).	Remarks.
May 5 . .	Injection of dye	8	
May 6 . .	Laparotomy; infection of peritoneum		
May 7 . .	Injection of dye	7	
May 8 . .	Injection of dye	8	
May 10 . .	Laparotomy; exploration; further infection		Moderate grade of peritonitis present
May 11 . .	Injection of dye	9	
May 12 . .	Injection of dye	9	
May 13 . .	Laparotomy; exploration; further infection		Severe grade of peritonitis present with considerable pus and many early adhesions
May 14 . .	Injection of dye	7	
May 15 . .	Injection of dye	9	
May 17 . .	Injection of dye	8	
May 19 . .	Injection of dye	11	
May 20 . .	Injection of dye	7	
May 22 . .	Injection of dye	10	
May 25 . .			Condition of animal poor for one week; now improving
June 2 . .	Injection of dye; laparotomy; exploration	8	Animal in good condition; many adhesions; no exudate or inflammation found; apparently severe peritonitis previously because of the numerous adhesions and thickening of peritoneum

Discussion. The injection of hypertonic solution of sugar intraperitoneally with the dye did not alter the time of appearance of the dye in the urine. Interchange of material must have been tak-

ing place simultaneously, both from the peritoneum into the blood and from the blood into the peritoneum. From these data the intraperitoneal injections of hypertonic solutions to retard absorption seems hardly justifiable as a treatment for peritonitis.

A comparison of the absorption rates of the dye from the peritoneum of normal rabbits, of rabbits with mechanical peritonitis and of those with bacterial peritonitis shows little difference. The average rate of absorption in rabbits with mechanical peritonitis was almost exactly the same as the average rate in normal rabbits. In rabbits with bacterial peritonitis, if those with the adhesive type of peritonitis are excluded, the average rate was almost exactly the same as in normal rabbits. The amount of variation in all three groups is essentially the same and the figures are, therefore, comparable.

There was very little difference in the findings in dogs and rabbits. The average absorption rates were almost exactly the same in normal dogs and in dogs with marked bacterial peritonitis. Occasionally the absorption rate was slightly longer than the average, but this seemed adequately explained by the presence of an adhesive type of peritonitis which had greatly lessened the area of peritoneal surface.

Summary. A brief review of the literature calls attention to the more generally accepted conceptions of peritoneal absorption.

Experiments on rabbits and dogs show that phenolsulphonephthalein is absorbed at essentially the same rate from the inflamed and the normal peritoneum, both in mechanical and bacterial peritonitis.

An exception noted was that an adhesive type of peritonitis greatly lessening the peritoneal area did seem to retard the rate of absorption slightly.

It was further concluded that the presence of hypertonic solution of sugar in the peritoneum did not retard the absorption of dye.

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THE SUCCESSFUL TREATMENT OF RESISTANT WHIPWORM INFESTATION.

WITH OBSERVATIONS ON OVERLOOKED SYMPTOMS.

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INSUFFICIENT attention has been given by gastroenterologists, or, for that matter, by the profession in general, to either the direct or indirect role played by intestinal parasites in the causation of morbid states of mind and body. Particularly is this true of infestation with the whipworm (*Trichuris trichiura* or *Trichocephalus dispar*). In his textbook on parasitology Stitt¹ remarks: "Whipworms do not, as a rule, produce serious symptoms. The patient may harbor parasites in considerable numbers for a long time without inconvenience. Rarely there may be a symptom-complex with severe anemia, pronounced nervous symptoms and gastrointestinal symptoms." Chandler² states that: "Although the whipworm

feeds on blood to some extent, and undoubtedly produces toxins, as evidenced by the increase of eosinophiles in the blood which nearly always occurs in case of whipworm infection and by the occasional mental disturbances or other nervous symptoms, this worm usually produces very slight, in fact, often unnoticeable effects." He further states that: "With the possible exception of hookworms and ascaris, the whipworm is the most common worm parasite in man."

The following paper is based on a study of 11 cases collected over a period of five years. In only 1 case did the patient's symptomatology arouse a suspicion of parasitism, and this was one of the last cases studied. The other 10 cases were simply accidental findings in routine feces examinations of patients suffering from various symptoms.

The only clue to the existence of whipworm infestation is the presence in the feces of dark-colored, oval-shaped eggs with knobs at either pole. The eggs contain the embryo. They are extremely resistant to most antiseptics and with sufficient moisture the egg embryo may live for years. The use of "night soil" as fertilizer is a potent way of contaminating food products. The mode of infection is through swallowing the ova. There is no multiplication of the worm within the body. The worm embryo arrives at maturity one month after ingestion, at which time it may produce eggs. The female whipworms outnumber the males and are somewhat larger than the latter which are less than 2 inches in length. The terminal portion of the worm is thread-like and usually curled up in a spiral. This whip-like portion burrows into the mucosa, thus making it very difficult to rid the intestine of the parasites. It is rarely that one finds the whipworm in the feces. The writer has seen them on several occasions during autopsies. The most common habitat of the whipworm is the cecum, but it is frequently found in other parts of the large bowel. It is supposed to be a frequent cause of appendicitis, though this is questionable. It seems highly probable that injury to the cell membrane by intestinal parasites either chemically, by means of both their secretions and excretions, or mechanically, by their sucking mechanism, allow toxic amines and bacteria or their poisons to enter more readily the circulation.

In the study of our 11 cases of whipworm infection it was noted that nervous symptoms were common to all. The series included 1 case of cholecystitis, 5 cases of chronic colitis—1 of which had multiple myeloma—and 1 case of diverticulosis. The remaining 4 cases showed no clinical pathology, though their symptoms would classify them as gastrointestinal invalids. These patients were all nervous high strung individuals, 4 of whom had consulted neurologists, who diagnosed their cases variously as neurasthenia, psychoasthenia, anxiety neurosis and hypomania. All of these patients

had capricious appetites, though, curiously, underweight was present in but 4 of the cases. All had gastrointestinal symptoms, such as marked flatulency, intestinal colic, constipation or mild diarrhea. One patient occasionally suffered from angioneurotic edema. Urticaria had occurred in 7 of the 11 cases. All patients showed marked pallor, and 2 showed a curious erythema covering the face and chest. Blood pressures were consistently low in all but the patient with cholecystitis. Abdominal examination revealed marked tympany in most instances and the cecal splash was present in every case. Proctoscopic and sigmoidoscopic examinations showed in most of the patients an injected, mottled mucosa streaked with mucus.

Stool Examination. In 9 cases the eggs were easily found. In the other 2 cases eggs were found only after repeated examinations by Barber's glycerin salt method.

Treatment. The time honored methods of parasite eradication by means of anthelmintics failed in all but 3 of our cases. Possibly this was due to the fact that all cases were in adults and infestation had either existed for a long time or was present in an intestine in which there were definite intestinal lesions. Oil of chenopodium with castor oil was tried in 4 cases with 1 cure after two trials. Hall and Foster's chloroform castor oil mixture was used in 7 cases, with 2 cures. The patients who were cured by the oral administration of drugs were those with acute symptoms and with no intestinal lesions discoverable by Roentgen ray or sigmoidoscopic examinations.

Our therapeutic hint which resulted in the cure of our 8 cases resistant to orthodox treatment was based on the assumption that the hair-like projection of the whipworm was embedded in mucous and possibly in the mucosa as well, and thus beyond the reach of drugs taken in the ordinary way. Our technique is briefly as follows:

At the beginning of treatment the patient is given 2 ounces of castor oil and then placed on a low residue diet. Then on each of four successive days he is given a 2-liter enema with 0.5 per cent solution of monohydrated sodium carbonate, to which is added 1 ounce of colloidal kaolin. Kaolin is also given by mouth in 1-ounce doses once daily on each of the above days. The alkali is given for the purpose of dissolving the mucus. The kaolin tends to cut the thicker mucus and mechanically "de-mucuses," so to speak, the wall of the entire colon. The kaolin likewise, by its mechanical adsorption, tends to sediment the bacteria which might possibly form a coating about the parasites. After this four day treatment the kaolin is discontinued, but the alkaline enema is continued for two days or more. After complete expulsion of this enema 8 ounces of crude oil is injected into the rectum through a large syringe and the patient instructed to retain it as long as possible. Proof that this small volume of oil reaches the cecum or even higher up is evidenced by the fact that for three or four days afterward the

patient continues to pass crude oil. In 2 cases fluoroscopic observations were made after the injection of a barium oil enema, and the preparation was seen to readily enter the cecum.

The results of treatment have been invariably successful in the cases studied. Fecal specimens immediately following the treatment and those examined a month later showed no eggs whatsoever. Four patients examined a year later showed negative findings. Two of the colitis patients entirely recovered from their colitis symptoms and were found free of all signs of whipworm infestation a year later. Stool examinations were made in 3 cases after the sodium carbonate kaolin enema series and prior to the oil administration, but eggs were still present, indicating that the oil is a necessary adjunct to the cure.

Summary. In the presence of structural change in the alimentary tract whipworm eradication, by means of anthelmintics, is practically impossible. The writer's colonic method was successful in the 8 patients so treated.

In all our cases of whipworm infestation a fairly definite symptom complex existed. Whether the infestation was superimposed upon an already existing pathologic colon, or had an etiologic relation to it, is difficult to say. A more scientific study of the pathology and symptomatology of whipworm infestation in its relation to to alimentary disorders is suggested.

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FURTHER REMARKS ON INFECTION OF THE GALL BLADDER IN RELATION TO CHRONIC (PERNICIOUS) ANEMIA.

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THREE years have elapsed since the writing of our former paper, "Infection of the Gall Bladder in Relation to Pernicious Anemia." In that study 13 cases of chronic anemia possessing some or all of the characteristics of idopathic progressive pernicious anemia were discussed. Of this number, 11 cases were recognized as frank per-

nicious anemia. Two cases were called borderline anemia, because megaloblasts were not found in blood smears and because the clinical picture did not present a progressive, or interruptedly progressive, downward course. These 2 cases possessed, however, a megalocytic type of anemia with a plus color index, complete achylia, glossitis and paresthesia. The blood picture differed little from that of the other cases, except in the severity of the anemia. Each of the 13 cases showed the presence of chronic infection of the gall bladder. The character of the infection of the gall bladder—and presumably that of the entire biliary tract, so far as could be determined—possessed no evidence of specificity.

The purpose of this report is to summarize briefly the subsequent histories of those patients upon whom cholecystectomy was performed, to add some data of further observations made upon similar patients and to state some general conclusions which the study seems to warrant.

Case Reports.—Former Series. CASE I.—(Borderline anemia.) Mrs. G., was readmitted in June, 1924, deeply jaundiced. The common bile duct was drained, and the patient made a slow recovery. Following the operation the blood counts dropped to 42 per cent hemoglobin* (Sahli-Haskins²); 3,380,000 erythrocytes and 7800 leukocytes, with many polychromatophilic red blood cells. In December, 1924, the patient had partially regained her former strength, but still showed a marked secondary anemia. The hemoglobin was 67 per cent; erythrocytes, 3,840,000; color index, 0.87; volume index, 0.96; leukocytes, 4750. There were no abnormal red blood cells present. Therefore, during the seven years following her first gall bladder operation there has been no return of her previously existing megalocytic anemia with a plus color index. In the summer of 1925 the jaundice returned, together with enlargement of the liver and beginning ascites. Death occurred from progressing chronic obstructive biliary cirrhosis in October of the same year.

CASE II.—Mr. C., following cholecystectomy in September, 1922, recovered partially during the winter of 1922–1923, and returned to his work of "cruising" timber. The paresthesia of his hands and feet, which had become acute immediately after his operation, disappeared completely for a time during the winter. The patient suffered a relapse in the late spring of 1923 and died in September of the same year. His blood examination prior to his death showed a true megaloblastic anemia of severe grade.

CASE III.—(Borderline anemia.) Mrs. K. has remained well since her operation in January, 1923. The blood continues to show the picture of secondary anemia, but the megalocytic character of it, which existed previous to her cholecystectomy has not returned. In November, 1924, her blood examination showed 64 per cent hemoglobin (Sahli-Haskins method); 4,050,000 erythrocytes; color index, 0.80; volume index, 0.92; icterus index, 5.7; 5500 leukocytes. The patient has experienced no paresthesia and the soreness of the tongue has disappeared.

* The figures for the percent of hemoglobin in the patients of the second series are not the direct readings of the Sahli-Haskins hemoglobinometer (on this instrument 100 per cent corresponds to 13.8 gm. of hemoglobin in 100 cc. of blood), but are so calculated that 100 per cent corresponds to 14.7 gm. of hemoglobin per 100 cc. of blood, the normal hemoglobin coefficient determined by Osgood.

TABLE I.—SEVEN CASES OF CHRONIC ANEMIA, SPOKEN OF IN TEXT AS BORDERLINE ANEMIA, WHICH CLINICALLY RESEMBLED MILD PERNICIOUS ANEMIA, BUT WHICH UNDERWENT SYMPTOMATIC RECOVERY AFTER REMOVAL OF INFECTED GALL BLADDER.

(Note Similarity of Clinical Data to Those of 4 Cases of Pernicious Anemia Listed in Table II.)

Case.	R. B. C. in millions.	Hb., per cent.	Macrocytosis polychromatophilia.	Nucleated red cells.	Color, Index.	Volume index.	Icterus index.	Achylia.	Glossitis.	Paros-thesia.	Duration of illness before operation.	Postoperative notes.
Case I (Series I)	3.68	85 (Dare)	+	0	1.16	+	+	+	7 years	Blood examination 9 months postoperative
Case III ¹ (Series I)	3.25	70 " "	0	0	0.76	0.96	+	0	0	1 year	Blood examination during obstructive jaundice
Case III ¹ (Series I)	3.84	64 (S. H.)	0	0	0.88	+	0	0		
Case III ¹ (Series I)	3.90	80 (Dare)	+	0	1.02	+	0	0		
Case III ¹ (Series I)	5.09	70 " "	0	0	0.70	+	0	0		
Case I ² (Series II)	4.05	64 (S. H.)	0	0	0.80	0.92	5.7	+	0	0		Blood examination 2 months postoperative
Case I ² (Series II)	4.00	66 " "	0	0	0.80	0.96	6.4	+	0	0		Blood examination 20 months postoperative
Case II d. (Series II)	1.38	15 " "	+	+normoblasts	0.55	1.20	2.0	+	0	0		Blood examination 3 years postoperative
Case II d. (Series II)	2.21	46 " "	+	0	1.00	1.20	5.0	+	0	0		Blood examination after transfusion
Case II d. (Series II)	3.10	63 " "	+	0	1.00	1.20	2.0	+	0	0		Death 4 days postoperative
Case III ¹ (Series II)	3.71	67 " "	+	0	0.90	0.96	5.0	+	0	0		
Case III ¹ (Series II)	4.36	75 " "	0	0	0.87	0.87	3.6	+	0	0		Blood examination 1 month postoperative
Case III ¹ (Series II)	3.90	86 " "	+	+normoblasts	1.10	1.20	9.1	+	0	0		Blood examination 10 months postoperative
Case III ¹ (Series II)	4.68	89 " "	+	0	0.96	0.99	6.0	+	0	0		
Case IV ¹ (Series II)	4.11	83 " "	tr.	0	1.01	1.02	10.0	+	0	0		Blood examination 1 month postoperative
Case IV ¹ (Series II)	3.85	50 " "	+	0	0.65	1.10	8.7	+	0	0		Blood examination 1 year postoperative
Case IV ¹ (Series II)	4.23	65 " "	tr.	0	0.77	1.07	6.6	+	0	0	Several years also	
Case IV ¹ (Series II)	4.32	70 " "	0	0	0.81	0.83	6.8	+	0	0	O. H. D.	Blood examination 1 month postoperative
Case IV ¹ (Series II)	4.14	50 " "	0	0	0.60	0.85	6.0	+	0	0	4 years together with	No change of anemia symptoms after hysterectomy
Case V ² (Series II)	4.52	62 " "	0	0	0.68	0.75	3.6	+	0	0		Blood examination 1 month after cholecystectomy
Case V ² (Series II)	4.26	86 " "	0	0	1.01	1.02	6.7	+	0	0		Blood examination 11 months after cholecystectomy

CASE IV.—Mr. H. was operated upon in May, 1923, and, as previously reported, a chronic infected gall bladder was removed. He recovered from the operation and returned to light farm work, but his blood never lost its megalocytic character. The soreness of the tongue disappeared; the numbness of his hands and feet, however, persisted. The patient suffered a relapse in February, 1924. He is still living, but has not been seen since this time.

CASE V.—Mrs. J., after having experienced the same symptomatic improvement in her general health noted by the other patients suffering from pernicious anemia following cholecystectomy, relapsed in October, 1923, and died early in the winter of 1924. The soreness of the tongue never returned.

We now give a brief description of 9 more cases of chronic anemia. Five of them we have placed in the borderline group and 4 we have considered true progressive pernicious anemia. Each case possesses a definite megalocytic anemia; anisocytosis, deformed cells and polychromatophilia. Two cases in the borderline group showed normoblasts in the blood stream; none of the cases in the pernicious group revealed any megaloblasts in many blood smears studied. A plus volume index was present before operation in all but 1 patient. The clinical data is given briefly in the subjoined tables:

Borderline Group.—New Series. CASE I.—Mrs. J., aged forty-eight years, a housewife, had been anemic and ill for three years. The illness became more acute in July and she was received in the hospital, August 4, 1924. She had the lemon tinted skin and the general appearance of pernicious anemia. Normoblasts were found in the blood stream, and the volume index was 1.2 on several occasions. Repeated blood transfusions raised the blood strength to 65 per cent hemoglobin and 3,000,000 red blood cells. A slow, continuous bleeding from some unrecognized point in the intestinal tract was present. The roentgenologic evidence of a diseased gall bladder was also obtained, and she was operated upon, September 20. The gall bladder was thick walled with many large, soft glands along the ducts; the appendix was thick walled and contained fecal stones; there were several small non-traumatic, hemorrhagic areas along the mesenteric side of the upper intestine from which the bleeding was taking place. The mesenteric glands were large and many of them calcified. Death followed on the fourth day. No autopsy was obtained.

Pathologic report: A pure culture of hemolytic streptococcus was obtained from the gall bladder. The appendix was atrophied.

CASE II.—Mrs. C., aged twenty-five years, a housewife, became pale and weak three years before, during a pregnancy. Her illness had slowly progressed until she had become completely incapacitated. She had the lemon tinted skin of pernicious anemia of moderate severity, but glossitis and paresthesia had not been present. Her teeth had been recently extracted for pericemental sepsis. The roentgenologic evidence of a diseased gall bladder was obtained and she was operated upon, January 6, 1925. The gall bladder was large, dirty grayish in color and contained stones. There were no other lesions noted in the abdomen. The gall bladder and a piece of liver were removed. The appendix had been removed at a previous operation.

TABLE II.—FOUR CASES OF PERNICIOUS ANEMIA CHARTED TO ILLUSTRATE SYMPTOMS SIMILAR TO THOSE OF CASES NOTED IN TABLE I.

Case.	R. B. C. in millions.	Hb., per cent.	Macro- cytosis poly- chroma- tophilia.	Nucleated red cells.	Color index.	Volume index.	Icterus index.	Achy- lia.	Glos- sitis.	Pares- thesia.	Duration of illness before any treatment.	Posttreatment notes.
Case VI (Series II)	2.93 4.04 3.95	70 (S. H.) 81 85	+	0	1.20	1.30	8.0	+	+	0	1 year +	Patient remains in fair health; able to work Blood examination 1 month after cholecystectomy
Case VII (Series II)	3.70 2.20 3.48 3.40 3.40 3.41 3.18	90 60 79 83 60 70 75	+	0 + normoblasts	1.07 1.20 1.30 1.16 1.20 1.25 1.00 1.20	1.19 1.30 1.40 1.05 1.20 1.36 1.40 1.10 1.20	5.6 5.7 6.2 7.6 6.7 8.1 6.2 6.6 8.1	+	+	0	1 year	Blood examination 9 months after cholecystectomy Blood examination 14 months after cholecystectomy Cord degeneration progressing Blood examination 3 months after cholecystectomy Blood examination 9 months after splenectomy Death from progressing anemia Blood examination during medical treatment before death
Case XI (Series II)	0.80 2.59 2.90	22 65 79	+++	0	1.37 1.35 1.30	1.70 1.40	10.0 10.7	-	+	+++	2 years	Blood examination 1 day before death Death from progressing anemia 1 year later Blood examination during medical treatment

Pathologic report: Chronic interstitial cholecystitis with fibrosis, scarring and lymphoid infiltration. Fatty or parenchymatous degeneration of marked degree of the liver; chronic interstitial hepatitis.

Cultures of the gall bladder wall and liver gave *Staphylococcus albus* in each.

Symptomatic recovery has taken place, but a moderate anemia of secondary type remains.

CASE III.—Mrs. B., aged forty-four years, a housewife, was first examined in 1917 because of a general asthenic state. Complete achylia gastrica was found at that time. In January, 1925, she returned because of numbness and tingling in the upper jaw and in both hands and feet. These symptoms had begun two years before, two months after the extraction of an abscessed right upper molar tooth. There had been no soreness of the tongue. Complete achylia was again found to be present. Roentgenologic evidence of a diseased gall bladder was obtained, and cholecystectomy and appendectomy were performed, January 28, 1925. The gall bladder was thick walled and adherent to the surrounding organs. The appendix was long and contained many fecal stones. The patient's health at time of writing (January, 1926) is quite normal. The numbness of the hands and feet disappeared quickly after operation. There have been no symptoms of glossitis.

Pathologic report: Chronic catarrhal cholecystitis. Fibrosis and hyalin degeneration of the appendix. No bacterial growths were obtained in cultures from the gall bladder and liver.

CASE IV.—Mrs. P., aged sixty-three years, a housewife, had been pale and weak for a number of years. She had suffered also for several years with dyspnea on moderate exertion in relation to a rheumatic mitral heart disease with auricular fibrillation without failure. Recently she had been confined to bed because of extreme exhaustion. The type of her anemia and the lemon tinted paleness of the skin made us suspect the presence of an underlying gall bladder disease. Stomach analyses were not made because of the presence of the heart disease. Definite numbness and tingling of the feet were present. There was no bleeding from the bowel. The patient was kept in bed for some time under dietetic and medicinal treatment for the anemia without benefit. On January 8, 1925, the gall bladder and appendix were removed. The former was thick walled and much enlarged; the common duct was dilated. A year has elapsed since operation. The patient is now stronger and in better health than she has been for years. The skin is clear and the lemon tint has disappeared. The heart action has quieted down; she no longer needs digitalis to control the auricular fibrillation. A moderate anemia still persists, but the megalocytic character of the red blood cells has disappeared and the volume index has dropped from 1.1 to 0.83.

Pathologic report: Atrophy and scarring of the gall bladder wall. Subacute purulent appendicitis of moderate grade, involving especially the mucosa, with plasma cell hyperplasia of the lymphoid tissue.

CASE V.—Mrs. C., aged forty-three years, a housewife, had been ill for seventeen years with mucous colitis. Diseased teeth and tonsils had been removed. In recent years she had become weaker and paler because of periodic bleeding from multiple myofibromata of the uterus. Her paleness was lemon tinted, however, and not of a whiteness due to bleeding. The tongue has been definitely sore at times, but no paresthesia has been present. Evidence of gall bladder disease was found roentgenologically. A supravaginal hysterectomy and appendectomy were performed on February 12, 1925, at which time the diagnosis of chronic cholecystitis was verified. The anemia and lemon tinted color of the skin did not improve

after operation. The patient remained weak; her convalescence was slow. Cholecystectomy was performed, March 27. Her response then was noticeably different from that following the first operation. Her skin cleared quickly and she improved rapidly in general health. The anemia, however, was slower to overcome. The soreness of the tongue disappeared and has not returned. She is in better health now than for years.

Pathologic report: Catarrhal and indurative cholecystitis. Cultures of the gall bladder wall gave a nonhemolytic streptococcus.

This patient differs from the other 4 patients of the borderline group in that the blood volume index has always been low, and also probably in the fact that ferments may have always been present in the gastric juice. Stomach analyses were not made during the acute period of the patient's illness. Later a normal stomach chemistry was found to exist. At the same time the blood volume index and the color index had returned to normal. This return to a normal blood picture has not been observed in the other cases. Whether there is a relation between the recovery of the normal blood picture and the absence of achylia is not known.

We have now under observation another patient of similar type: A man, aged fifty years, who has been anemic and ill for two years. He suffers from weakness, dyspnea on exertion, periodic soreness of the tongue, numbness of the fingers and periodic nausea, vomiting and pain in the abdomen. His case has the appearance of pernicious anemia, and his illness has been so considered by some physicians whom he has consulted. His blood examinations give, on an average, the following figures: Hemoglobin, 46 per cent; red blood cells, which are very irregular in size and shape, 2,700,000; white blood cells, 7000; color index, 0.85; volume index, 0.86; icterus index, 2.2 (in spite of the presence of chronic cholecystitis). The fasting stomach contains free hydrochloric acid and no food remnants. An Ewald breakfast shows 55 free hydrochloric acid and 74 total acidity, with well chymified food. No improvement in the patient's condition could be brought about by medical treatment in hospital, and as positive roentgenologic evidence of a diseased gall bladder was obtained, cholecystectomy has recently been done.

The 4 remaining cases of this series are examples of true progressive pernicious anemia. They differ from the others clinically, however, only in the degree of anemia, and, in the 2 patients upon whom cholecystectomy was performed, in the failure of noticeable relief after operation. The blood volumes also ranged higher in these patients and did not drop so low after operation; but, again, this variation may be but a matter of degree.

Pernicious Anemic Group.—New Series. CASE VI.—Mrs. E., aged fifty-one years, a housewife, was seen first in January, 1925. She had been pale for years, but during the past year the paleness had increased, soreness of the tongue had appeared and she had lost in weight and strength. On examination, the patient showed the presence of glossitis, complete achylia and a megalocytic blood picture. The roentgenologic evidence of a diseased gall bladder was obtained, and this organ, together with the appendix, was removed, February 17, 1925. The gall bladder was thick walled, with many small papillæ like nodules growing into its lumen. The common duct was not enlarged, but there were many soft glands along its course. Cultures of the gall bladder wall were sterile, except for four colonies of a short Gram positive bacillus. A piece of liver cultured showed several colonies of *Staphylococcus aureus*. Specimens of stool and scrapings from the tongue were cultured for yeast, being grown on a modified Sabouraud

medium, as suggested by E. J. Wood.³ From each source yeast cells were obtained which were grossly; microscopically and culturally identical. After forty-eight hours culturing at 30° C. small, yellowish white, glistening colonies appeared, which, microscopically, showed large, rapidly growing yeast cells with many buds but no hyphæ. Culturally on sugars they reacted as follows: Maltose, acid, no gas; lactose, negative; glucose, negative; litmus milk, coagulated. The organism was not considered *Monilia psilosis*.

Since the operation the patient has improved very much in health and strength. Her skin has cleared and the lemon tinted color has disappeared. She is not as well or as strong as she was two years ago. The glossitis comes and goes. She has never suffered from paresthesia. Many macrocytes remain in the blood stream and the blood volume remains slightly above 1.

Pathologic report: Chronic cholecystitis. Moderate atrophic appendicitis.

CASE VII.—Mr. P., aged sixty-six years, a merchant, was first examined in 1914, when a complete achylia gastrica was found. On a corrective diet and hydrochloric acid he became free of symptoms and remained well until one year before he returned for reëxamination in January, 1925. For a year he had been losing weight and strength. He had become pale, short of breath and periodically had suffered from numbness and tingling in the hands and feet and soreness of the tongue. His skin was pale and lemon tinted in color; his tongue slick with reddish patches; the achylia was still present; his blood was macrocytic in type with a volume index of 1.4 and occasional normoblasts. The reflexes were normal. Roentgenologic evidence of a diseased gall bladder was obtained, and he was operated upon, February 16, 1925. The gall bladder was thick walled and adherent to the hepatic flexure of the colon and the duodenum. The spleen was much enlarged. It was estimated to be about four times its normal size. The gall bladder and appendix were removed at this time. Following the operation the blood picture did not change much in its appearance, although the hemoglobin reached 88 per cent and the red cell count 4,000,000 per cubic millimeter. The color of the skin cleared a good deal, though not as it had in the other patients. A moderate relapse began in the summer, so that it was thought justifiable to remove the spleen. This was done, August 10, 1925. The spleen was now found to be about one-third its former estimated size as seen in February.

Since the last operation the patient's convalescence has been about as it was after the cholecystectomy. The skin is much clearer and the lemon tinted color has nearly disappeared, but aside from this fact there is little change. The anemia and the glossitis remain as before. The degenerative cord changes are progressing. Megaloblasts have never been found in the blood. He is now receiving blood transfusions.

Cultures made from the gall bladder on blood agar plates and in blood dextrose broth gave colonies of *Staphylococcus albus*. Similar cultures from the spleen gave hemolytic *Staphylococcus aureus* and *Staphylococcus albus*. Cultures were also made in this patient from tongue scrapings and from the stool as in Case VI. Microscopically the yeast obtained in these cultures resembled very closely that obtained in the latter case, but had a different reaction upon the sugars. There were no demonstrable hyphæ present. After forty-eight hours' incubation at 30° C. small, whitish, glistening colonies appeared. Microscopically, large celled, rapidly budding yeast cells without hyphæ were seen. Culturally, on sugars, the following occurred: Lactose, negative; maltose, acid and gas; dextrose, acid and gas; milk, no change. Seemingly the same organism was obtained from both the tongue scrapings and from the stool. It, likewise, was not considered to be *Monilia psilosis*.

Pathologic report: Chronic cholecystitis. Slight diffuse chronic hyperplasia of the spleen.

CASE VIII.—Mrs. R., aged sixty-seven years, a housewife, was first under treatment in 1914 for a general asthenia in relation to a complete achylia gastrica and constipation. The last few years she has had occasional pain of slight degree under the right costal margin. Myositic pains of the neck and left shoulder girdle ceased after the removal of her tonsils and several devitalized teeth one year ago. She was reexamined and under hospital treatment in August, 1924. For over a year she had complained of dyspnea on exertion and slowly increasing general weakness. She has had periods when her tongue was sore, but had had no sensory disturbances. Her blood picture was megalocytic in type. The blood volume was at first 1.4, but returned to 1.1 under bedrest, arsenic, and so forth, during which time she also improved much in general health and strength. In December, 1925, she suffered a relapse, during which time sensory disturbances became marked, and her blood picture was: Hemoglobin, 42 per cent; red blood cells, 1,960,000 without nucleated cells; volume index, 1.6; color index, 1.2; icterus index, 6.6. Death occurred a few weeks later. Autopsy was not obtained. The roentgenologic evidence of a chronic gall bladder disease was present. It is interesting, furthermore, to note that the patient was a sister of the patient, Case XI, of the first series, and that a second sister is now ill with pernicious anemia with marked cord changes. (See papers of Meulengracht⁴ and others.)

CASE IX.—Mr. S., aged sixty-two years, a business man, was under examination and treatment in the summer of 1924. His case is cited because it was a frank, rather rapidly progressing type of pernicious anemia with marked degenerative cord lesions, without, however, a megaloblastic type of anemia, and with positive roentgenologic evidence of chronic gall bladder disease obtained on two different examinations. The patient died in August, 1925. Autopsy was not obtained.

Discussion. In the description of the two groups of anemia patients recorded in this paper and in the former paper, a marked similarity in the type of anemia and in the physical findings on examination is noted. A chronic lytic anemia existed in each patient except for the presence of megaloblasts, which were found in only 3 of the 21 patients studied clinically during life. The skin of each patient showed lemon tinted paleness and in all except 1 patient achlorhydria was present. Glossitis occurred 13 times and subjective symptoms of cord changes were experienced 14 times. Evidence of a diseased gall bladder were found by roentgenologic methods in each patient examined clinically, and these findings were verified by the pathologist in the patients coming to operation. Disease of the biliary tract was found also in the cases which came to autopsy.

More upon intensity of the symptoms than upon difference of clinical picture, the cases were divided into two groups, namely, those of frank progressive pernicious anemia and those which we have spoken of as borderline anemia. We called the picture a borderline anemia because the blood was megalocytic in type, because other causes for the anemia were not found and because the patients did not progress to a fatal issue after cholecystectomy,

but returned, on the other hand, to fairly normal health, in which the so-called pernicious characters, as represented by the blood, skin, tongue and sensory disturbances, disappeared. A return of gastric ferments was not observed. (Note that Case V, second series, may be an exception.)

During the study of the first series of cases an attempt was made to produce a chronic anemia in dogs by producing chronic infection of the biliary tract by means of organisms obtained culturally from the gall bladders and livers of some of the patients. Negative results were obtained. Insofar as they could be judged, the organisms seemed to be nonspecific. Similar types of organisms were obtained from patients of the second series. In 2 cases of pernicious anemia tongue scrapings and stools were cultured for yeast, according to the suggestion of Wood. Yeast cells were obtained in each case, but they could not be identified as *Monilia psilosis*, which has been connected by Ashford with sprue.

The fact that the biliary tract of each patient of both series proved to be infected is of outstanding interest. Whether the infection was simply one of many focal infections existing in the body or whether it has a deeper meaning remains to be proved. As one theorizes about the cause of the two arbitrarily designated anemias, one recognizes the necessity of the presence of some hemolytic agent or agents which operate continuously over a variable length of time, and produce in the pernicious group, at least, hyperplastic changes in the bone marrow. We have not had opportunity to study the bone marrow in any of the cases of the borderline group. To think of these anemias as being the result of widespread focal infections from a dental, a lingual or other source, as some writers have held, is not logical, because such infections are almost universal; but it is logical to believe that an infection, or other disease process, operating in a special way from a special site, may produce such an anemia. The fact that lytic substances causing the pernicious anemias of *Bothriocephalus latus* and of hookworm infections are said to be lipoid in character, and that a megaloblastic anemia may be caused in rabbits by using a similar agent, suggests the possibility that changes in the cholesterol content of the bile, by means of organisms possessing special properties and operating in constant contact with it, may be a possible cause. The question of hereditary factors as seen in families in relation to a constitutional pathology does not detract from the credibility of such an hypothesis. Unquestionably, however, proof supporting such an hypothesis is wholly lacking. The supposition must rest for the present upon the meager clinical evidence afforded by the study of such cases as these recorded here.

What, then, is the clinical evidence upon which a causative relation between chronic infection of the biliary tract and a chronic lytic anemia may be surmised? In the first place, constant achlorhydria is present. Just what the presence of achlorhydria may

mean is not known, but it seems to be the ground upon which a group of chronic diseases are related. In this category pernicious anemia has always occupied an important place. Again, the anemia is essentially chronic, although variable in its intensity. This variable characteristic of the disease strengthens the belief that one is dealing with the same underlying mechanism in the two groups, for all gradations in symptoms and course are found, from the rapidly fatal pernicious type to the type which causes the patient to drag on through many years, to die finally from true pernicious anemia or to succumb to some intercurrent infection. The cases spoken of above as borderline anemia are of this latter type. There is no clinical means known at present by which a closer differentiation can be made. The volume index of the blood, upon which some writers place much reliance, shows the same variations in degree.

A close scrutiny of the remaining clinical symptoms of the two groups does not lend any aid toward segregation. There is found the same variation in degree in these symptoms that one sees in the progress of the disease itself. The soreness of the tongue comes and goes in patients of each group. The same is true of the sensory disturbances. Both symptoms are only more severe and more persistent in frank pernicious anemia. Periods of relapse and partial recovery occur less noticeably in the borderline group than in the other, but they nevertheless occur. Normoblasts and microblasts occur in the blood stream with moderate frequency in the borderline type and megaloblasts are often entirely absent throughout the course of true pernicious anemia. Aside from the giant nucleated red blood cells, however, there is no difference in the blood picture of the two groups except in degree. A high blood volume index, as first noted by Capps,⁶ has been considered to be of special significance in the differentiation of true pernicious anemia from other types of anemia.* In the borderline group a blood volume index

* For the proper interpretation of blood analysis figures clinical methods must be used which reasonably stand the test of research accuracy. The methods employed with the patients of the second series are as follows: (1) Hemoglobin estimation: The Haskins modification of the Sahli hemoglobinometer with which a permanent standard made of an aqueous solution of ferric sulphate and cobalt sulphate is used, the pipette and tubes being correctly calibrated. This method gives results within 2 per cent of the correct amount (*J. Biol. Chem.*, 1923, 57, 1). (2) Blood volume index: Venous blood, prevented from coagulation with potassium oxalate in proportion of 20 mg. per 10 cc. of blood is centrifuged inaccurately calibrated tubes, at 4500 revolutions per minute, until there is no further change in the volume of the packed cells noted on repeated centrifuging. The specimen is centrifuged in five-minute periods. From thirty to sixty minutes is usually necessary to obtain constant readings. The volume index, according to Osgood, varies between 0.85 and 1.15 in 90 per cent of the bloods of normal men. The color index varies also between 0.85 and 1.15 in similar bloods. (Osgood: Hemoglobin, Color Index, Saturation Index and Volume Index and Volume Index Standards, *Arch. Int. Med.*, 37, 1926, 685.) (3) Red blood cell counts have all been made on the patients of the second series with the same hemocytometer. These estimations, as well as those of the blood volume and the hemoglobin have been frequently checked, for the sake of greater accuracy, by Dr. Osgood and Dr. Holbrook of the Department of Biochemistry.

of 1.2 is not uncommon, and in true pernicious anemia the same index may be lower than 1.1. In one patient dying of uremia we noted a blood volume index of 1.3 and 1.4. The pathologist's post-mortem findings in this case were cardiorenal disease, arteriosclerotic kidney, fibrinous pericarditis and extreme hyalin degeneration of the spleen, liver and adrenals. There were no noteworthy gross changes in the marrow of the long bones.* The relatively high volume content of the red blood cells may be a group reaction and in no way a specific one.

The response of the patient to removal of the infected gall bladder in both groups is suggestive of a causative relationship. In frank pernicious anemia cholecystectomy may produce a profound betterment for a time. The skin will clear, the glossitis and paresthesia may disappear and the patient will temporarily improve. The blood volume index may drop to 1 or even below 1. The pernicious type of the blood, however, does not disappear. Relapses have occurred as before and death of patients who were operated upon three or more years before has finally resulted from the anemia. In Case VII, in which splenectomy was performed, the previous removal of the gall bladder had a profound effect upon the condition of the spleen.

In the 6 patients of the borderline group removal of the infected gall bladder has had the same beneficial effect upon the immediate clinical picture. The improvement is more pronounced and thus far has been permanent in 5 of the 7 cases listed. One of the remaining 2 patients, after six years of ordinary health, developed a persistent common duct obstruction that resulted in chronic obstructive biliary cirrhosis of the liver; the other patient died shortly after operation from continued bleeding. The remaining 5 patients all have shown the following changes: The skin has lost its lemon yellow color; the blood picture has changed from one with numerous macrocytes, irregularly stained cells, and plus color index, to the picture of moderate secondary anemia; the blood volume index, when it was above normal, dropped below 1 and remained there. Of all symptoms, the anemia has been the slowest to disappear. The soreness of the tongue and the paresthesia have disappeared quickly and have not returned. There has been no return of the previous relapses. The achlorhydria has thus far been persistent. Nevertheless, the patients either consider themselves now well, or feel that, the cause of their illness having been removed, they are becoming progressively better. Data regarding their general

* Histologic examination of the bone marrow in this case shows little or no hyperplasia. There is, however, a greatly increased number of eosinophilic myelocytes and a moderate increase of megaloblasts. There is evidently some blood destruction, but even the increase in megaloblasts is hardly great enough upon which to base a diagnosis of pernicious anemia. The history of the patient during life was that of cardiorenal disease. To correspond with the increase in eosinophilic cells in the bone marrow there was no history, on the other hand, of asthma, or of intestinal parasitism, and three differential blood counts showed no eosinophilia.

appearance, body weight and blood examinations, periodically obtained, substantiate these beliefs.

A study of the patients of the two groups impresses one with the possibility that a mild and a more severe grade of the same disease is being considered. Wood has made the interesting observation that feeding to guinea pigs a culture of *Monilia psilosis* obtained from cases of pernicious anemia produced a hemolytic blood picture with hyperplastic bone marrow changes; that the filtrate of the culture given intravenously produced the same hemolytic blood picture in less marked degree; that the giving of smaller amounts to the animals produced similar changes, from which the animals recovered when the injections were discontinued.

Pernicious anemia is doubtless a group of diseases. From time to time a specific cause of chronic hemolytic anemia has been recognized, and a small group of cases split off from the main group with unknown causes. It seems to us quite justifiable to suspect that in the segregation of the cases above recorded into true pernicious anemia and borderline anemia, we have been working with a hemolytic type of anemia of unknown cause, but related in some way to chronic infections of the biliary tract; that, by the removal of, possibly, the main focus of infection, mild cases may have recovered; that in the more severely infected cases, which go on to death, the hemopoietic centers of the bone marrow simply may have been damaged beyond repair, or that further extension of the infection in the liver may have permitted the continued formation of the same lytic bodies. The hypothesis that such an infection may cause anemia through changes in the cholesterol content of the bile is attractive.

Conclusions. 1. In every case of pernicious anemia with which we have personally worked during the time of this study, a chronic infection of the gall bladder has been positively demonstrated.

2. A small group of cases, which resembled mild pernicious anemia, possessed the same type of biliary infection, and upon its removal the patients were restored to fairly normal health.

(The pathologic and bacteriologic studies recorded in the above paper were made in the department of pathology under the guidance of Dr. Robert L. Benson, to whom we wish to acknowledge our indebtedness.)

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THE INTRADERMAL SALT SOLUTION TEST IN SCARLET FEVER.*

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THE intradermal salt solution test, as described by McClure and Aldrich¹ is carried out by injecting intradermally 0.2 cc. of a sterile 0.8 per cent aqueous solution of sodium chlorid, and recording the time necessary for the disappearance of the wheal so formed. The wheal is considered to have disappeared when it can no longer be detected by light palpation. In normal persons the time required is sixty minutes or more, while in various diseases it is reduced. McClure and Aldrich^{1, 2} reported occurrence of shortened disappearance times in children with edematous and præedematous conditions, especially those with associated albuminuria. Baker³ found shortened disappearance time in scarlet fever and diphtheria patients; Harrison,⁴ in children with lobar pneumonia; Olmsted,⁵ in cardiac disease in children. Cohen,⁶ and Cohen, Applebaum and Hainsworth⁷ used the test as a means of determining the efficiency of the circulation in the extremities in peripheral vascular disturbances of the sort that may lead to gangrene. Lash⁸ reported the finding of a markedly shortened time in toxemias of pregnancy. It has been suggested that increased rapidity of absorption of the injected salt solution may be related, in some conditions studied, to tissue intoxication resulting from infection or circulatory disturbance.

Intradermal salt solution tests were carried out on 60 scarlet fever patients. The wheals were observed until they disappeared, unless they persisted longer than sixty minutes. Times of sixty minutes or more were considered normal. A test was made when the patient entered the hospital, usually between the second and eighth day of the disease, and was repeated at intervals of a few days thereafter, usually until the disappearance time became normal. The wheals were made on the arm and leg, or sometimes on the arm alone.

The present series represents cases of scarlet fever of more than average severity, as only a few patients with mild attacks were tested. Most of the patients showed a shortened disappearance time at the first test, with the amount of shortening roughly proportional to the degree of toxemia and the height of the temperature. Those who were only slightly ill with slight elevation of temperature, had normal or nearly normal times. In moderately severe cases the time was usually between thirty and forty minutes. There were exceptions, however; for example, a fairly sick patient,

* This work was done at the Annie W. Durand Hospital of the John McCormick Institute for Infectious Diseases under the auspices of the Otho S. A. Sprague Memorial Institute.

with temperature of 102° F., had a normal disappearance time; one, only mildly sick with temperature of 99.6° F., had a time of twenty-three minutes. In all of the very sick patients, about 10, of either toxic or septic type, the wheal disappeared rapidly, in six to thirty minutes. The shortest time observed was six minutes. This was in an adult who entered the hospital on the sixth day of illness. He was exceedingly toxic, irrational much of the time, with an intense rash, temperature of 104.2° F. and a very low output of urine containing albumin, casts and blood. There was no palpable or visible edema. He died the next day. Three other patients, all very sick, had disappearance times below twenty minutes in the first week of illness. Only one of these had albuminuria and none had palpable edema.

The shortened disappearance times, as a rule, returned rapidly to normal in the absence of complications. Since the tests were not made daily, the first day of normal time is not known, but in uncomplicated cases, in which tests were done at intervals which permit the drawing of conclusions, approximately 75 per cent had reached normal by the eleventh day. Frequently the disappearance time became normal before the temperature, but occasionally this relation was reversed. In only 2 or 3 instances were the patients apparently well and ready to get up, as far as the clinical condition was concerned, before the disappearance time had become normal. In one patient apparently well, in whom the disappearance time seemed slow in reaching normal, whooping cough developed during convalescence from the scarlet fever.

The complications of scarlet fever may not be accompanied by a reduction of disappearance time. Two cases of otitis media and one of arthritis occurred without any reduction. However, the septic patients with high fever and general prostration had shortened times during the febrile period.

A case of moderately severe postscarlatinal nephritis was observed in a boy, aged six years, who had been only mildly sick at first. No tests had been made during the acute stage of the scarlet fever. On the eighteenth day there were blood, albumin and casts in the urine, with a slight rise in temperature. The disappearance time was then forty-three minutes for the arm and twenty minutes for the leg. During the next few days severe headache, vomiting and edema of the legs and back were present. The time on the twenty-second day was forty minutes for the arm and ten minutes for the leg. The following day the output of urine was only 75 cc., the lowest at any time. The patient improved, the output of urine increased and the disappearance time rose gradually and reached normal on the thirty-third day of illness. There was still a trace of albumin, and a few casts and blood cells in the urine.

Another patient, aged four years, not tested at first, had blood cells in the urine and vomited on the twenty-fifth day of his illness,

when his disappearance time was fifty-five and fifty minutes for the arm and leg respectively. Two days later, with albumin, casts and blood in the urine, the time had fallen to thirty-three and thirty-seven minutes. The patient recovered very rapidly, with the disappearance time reaching fifty minutes on the thirty-first day. A child, aged seven years, with a mild course, had slight fever, with albumin, casts and blood in the urine, without edema or subjective symptoms on the nineteenth day. The disappearance time was thirty-five minutes for the arm and leg, whereas it had previously been forty and sixty minutes for the arm and leg respectively. On the thirty-first day the urine was normal and the time for the arm was sixty minutes. In 2 other instances mild nephritis, manifested only by traces of albumin and a few blood cells in the urine, without rise of temperature or symptoms, was not accompanied by reduction in the disappearance time.

Nine patients who were given scarlet fever antitoxin (at first that made by the Drs. Dick, later Squibb's preparation) were tested before, and again ten hours to two days after, injection. The increase of the disappearance time during the ten hour to two day periods immediately following the serum injections was not materially different from that seen during similar periods and day of disease in patients who did not get serum. About the same proportion of 14 patients who received antitoxin became normal within ten days as of those who did not receive antitoxin; but this represents a relatively more rapid improvement in the persons given antitoxin, since they as a group were much sicker.

Ten of the 14 patients given antitoxin had initial disappearance times; on either arm or leg, of thirty minutes or less. The test may be of help in deciding whether or not patients should be given antitoxin. Although the correspondence between the shortening of the disappearance time and the severity of the illness is not always exact, a time below thirty minutes may be considered as an indication for giving antitoxin.

Serum sickness with severe urticaria in 3 patients was accompanied by shortened disappearance time. In 1 the time dropped from forty-five to twenty-seven minutes with appearance of the urticaria, in another from sixty to thirty-five minutes and in the third it was twenty-four minutes at the onset of the urticaria.

The results of the tests on the arm and leg were approximately the same in the majority of instances. Where there was a discrepancy, disappearance from the leg was usually more rapid, possibly due to accompanying circulatory disturbance. For example, a patient who developed myocarditis in the second week had a disappearance time for the arm of fifty minutes and for the leg twenty-three minutes. A man who was on his feet and working through the first few days of illness, and had some edema of the legs, had an

arm time of sixty and a leg time of twenty-eight minutes on the fifth day. The urine was negative.

Summary. The time required for disappearance of the wheal made by injecting salt solution intradermally was found to be shortened in scarlet fever, with the amount of shortening roughly proportional to the severity of the illness. In the absence of complications the time returned to normal rapidly, usually before the patient was ready to be out of bed. Urticaria was associated with a shortened disappearance time. A disappearance time of less than thirty minutes may be taken as an additional indication, besides the patient's general condition, for giving scarlet fever antitoxin.

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HEMIHYPERTROPHY AND TWINNING.

A FURTHER STUDY OF THE NATURE OF HEMIHYPERTROPHY WITH REPORT OF A NEW CASE.

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"If it is in her moments of abnormality that Nature reveals her secrets, as Goethe once remarked, then the condition of hemihypertrophy assumes an added piquancy of interest. It is one of the rarest of medical anomalies and of such character that it might well disclose some glimpse of the inner mechanics of development.

It is essentially a developmental anomaly. It antedates birth and arises in some way as a partial deflection of the normal processes of growth. It strongly suggests a curtailed form of double mon-

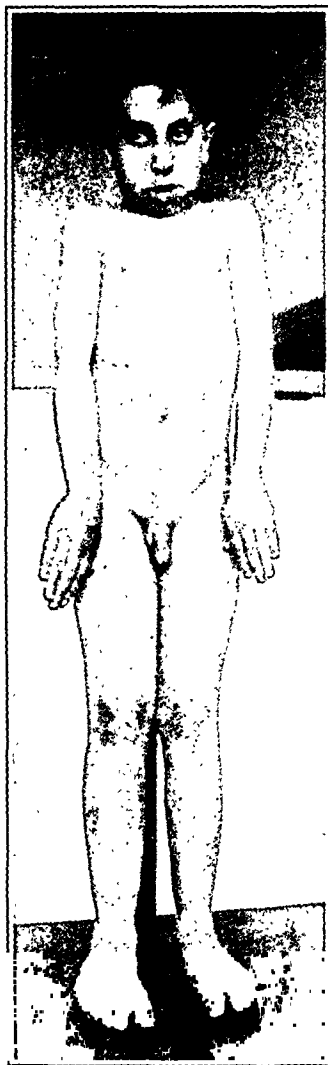


FIG. 1.—Hemihypertrophic Case I (S. D.), aged thirteen years. (See Archives of Neurology and Psychiatry, 1921, 6, 400.)

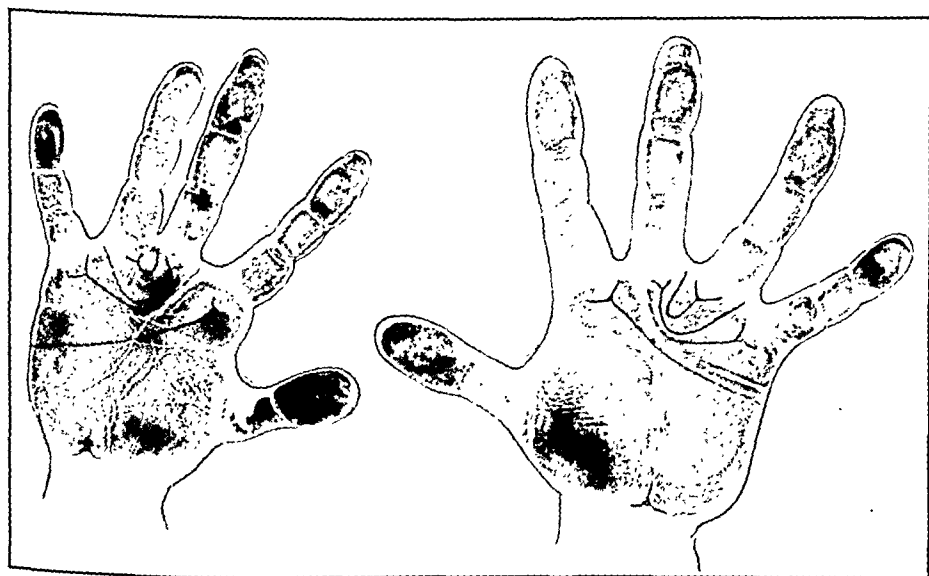


FIG. 3.—Palm prints of left and right hands of Case I. Showing disparity in size, but identity in the configuration of the friction ridges. The pattern formula for these ridges derived by Wilder's method is in each hand: 11 - 9 - 7 - 5 - C.

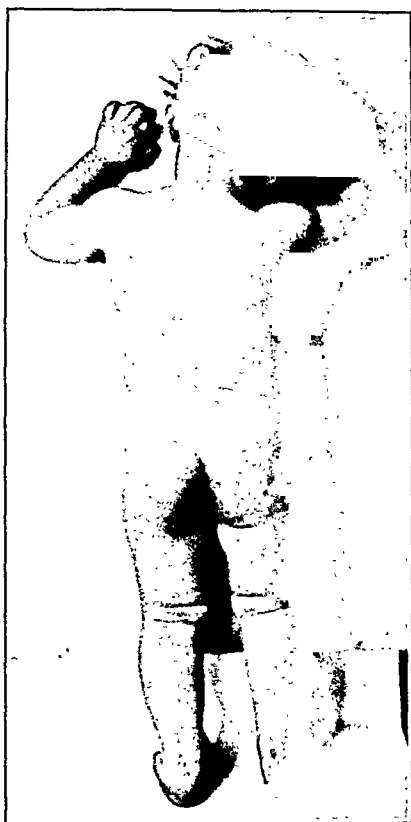


FIG. 4.—Hemihypertrophy, CASE II. Aged two years.

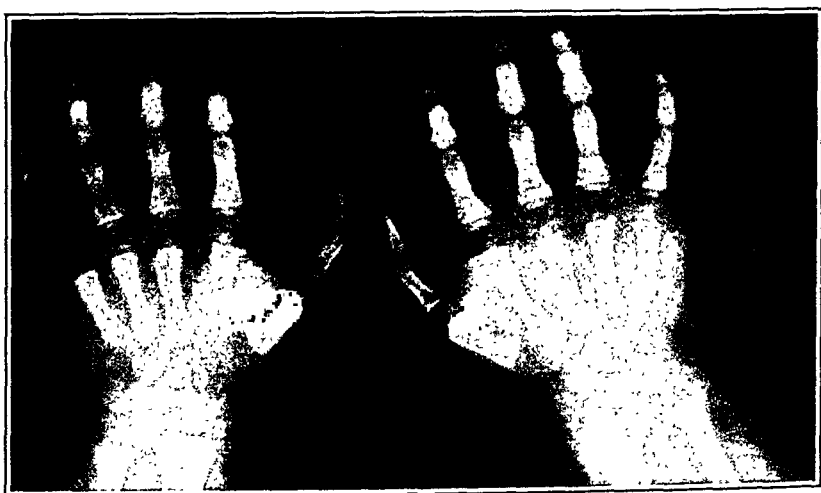


FIG. 5.—Roentgen ray of hands of CASE II. Aged two years.

strosity. It is a mild degree of gigantism, curiously confined to one side of the body. It is a unilateral enlargement of one-half of the soma, a hemimacrosomia. As such we may interpret the condition to be an atypical or a paradoxical form of twinning, a hybrid variant of the same process which may produce a double monster or a completely symmetrical individual. The biologic paradox consists in this, that the hemihypertrophy is neither double monstrosity nor bilateral duplicity; it is half of each, as though the individual remained two conjoined hemicreatures, each with a discrete though half realized genetic destiny.

In 1921, I reported a case of hemihypertrophy, associated with mental defect in a boy examined at thirteen years and again at twenty years of age. A few further observations on this youth reexamined at the age of twenty-five years are reported below.

In view of the extreme rarity of well-defined hemihypertrophy, the laws of probability should scarcely permit another case to come unsought to our clinic. It was, therefore, a matter of great surprise to find the same condition repeated in a two-year-old girl who was referred to us on account of slowness and difficulty in walking. Perhaps the laws of chance were slightly weighted in our favor, because many of the children referred to the clinic are mentally deficient; and it was the thesis of our earlier paper that mental defect of some degree is found with disproportionate frequency in association with hemihypertrophy. It happens that in our second case this same association is repeated, confirming the suggestion previously made "that hemihypertrophy should be added to the list of developmental anomalies which bear some lawful relation to the incidence of mental deficiency."

Case Reports. CASE I.—S. D. male, examined at ages thirteen and twenty years, reexamined at twenty-five years, has been under our observation for twelve years. (See Fig. 1.)

The subject was first examined when a boy aged thirteen years, and again at the age of twenty years. He presented a well-defined total unilateral hypertrophy of both soft and hard tissues on the right side, with characteristic port-wine telangiectatic patches of the skin, and definite mental defect.

The details of this case were reported in a previous article and need not be recapitulated. We recently renewed our acquaintance with this youth when he had reached the age of twenty-five years. This reexamination furnished a few supplementary observations.

Physical remeasurements showed that there has been no change since the age of twenty. Height remains the same (67 inches). Length measures of arm, forearm and leg also remain as before. There has been a slight increase in weight, with associated increase in individual girth measures; but there has been no actual change in the degree of disparity. Morphologically, therefore, we may

conclude that in a period of twelve years the condition of hemihypertrophy has shown no progressive or equalizing tendency.

Psychologically, also the status of this case has remained remarkably constant. We made a rather detailed psychometric comparison of his mentality at the ages of twenty and twenty-five years, and found a thoroughgoing degree of correspondence in the behavior pictures of these two ages. The almost unmitigated lack of either deterioration or advance suggests that hemihypertrophy represents a well-ballasted deviation, in spite of the fact that differences of a physiologic character have been noted in the two sides.

At the age of thirteen years, S. D. had a mental age of four and a half years, yielding an intelligence quotient of thirty-five. Assuming that general mental maturity is attained or nearly attained at the

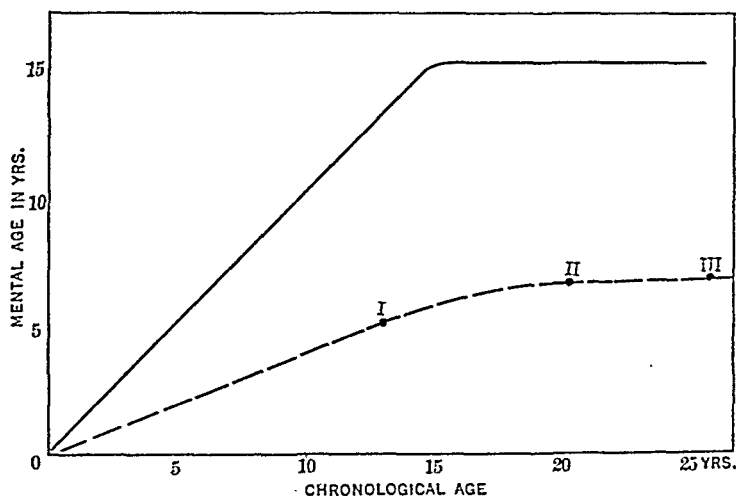


FIG. 2.—Mental growth chart of CASE I (S. D.).—The solid line shows the diagrammatic normal line of growth as measured by mental age. The broken line represents the approximate course of growth of S. D. as shown by mental-age ratings made when he was thirteen, twenty, and twenty-five years of age.

chronologic age of sixteen, he receives at the age of twenty-five, precisely the same mental rating, with a mental age of five years, eight months and an I. Q. of thirty-five. With a few minor exceptions there was virtual identity even in the individual test items of the examinations at twenty and at twenty-five years.

In 1921 he was asked: How many fingers have you on the right hand? On the left hand? On both hands? His answers were 7, 7, 8. In 1926, his answers were 7, 7, 14. In 1921, he spelled and misspelled as follows: *cat*, *house*, *it*, *Mew Haren*, *Spelling*, *Arithnetic*. In 1926 his orthography for these words was exactly the same, except that *it* was spelled *ta*.

Additional interesting details might be cited to show the permanence and completeness of the mental retardation, and the consis-

tency with which it has revealed itself in the past twelve years. The chart summarizes diagrammatically the character of this mental growth and subnormality. (See Fig. 2.)

Palm prints were made of the left and right hands of S. D. to determine whether there is any significant difference in the configuration of the friction ridges. These ridges appear as early as the fourth month of intrauterine life, and it seemed worth while to inquire whether the condition of hemihypertrophy had impressed any marked atypicality upon them. When mapped by Wilder's method, the ridges showed considerable identity of pattern. The pattern formula in each hand is 11-9-7-5-C. The only striking disparity is one of size. (See Fig. 3.)

CASE II.—M. S., female, was examined at ages two, three and four years. (See Fig. 4.)

Physical Development. This girl is a first child, with a negative family history, born normally (reported weight, 10 pounds). Was breast fed for eighteen months. No unusual illness known. One episode of convulsions, attributed to a digestive disturbance, reported at the age of two years. First tooth erupted at nine months. Walked at twenty months.

She walked with difficulty, frequently stumbling, and limping perceptibly. This was one reason why she was referred to our clinic. The limping proved to be due to the disproportionate length of the left leg. The disparity was sufficiently marked to cause the orthopedic clinic to recommend a built-up shoe for the right foot. Since then the motor difficulty has been largely overcome; but it caused much embarrassment in the early stages of walking.

Physical inspection as well as measurements showed that the asymmetry was of a total unilateral character, and that the whole left side was hypertrophied. Roentgen ray photographs showed that the bony as well as soft tissues were involved. The tongue was markedly hypertrophied to the left of the median line, and there was a definite corresponding convexity in the left lateral aspect of the tip. The tongue deviated to the right side on extrusion. (See Fig. 5.)

To ordinary inspection there was no difference in the teeth. There were eight on each side, with caries more advanced on the left side. The left half of the nose and the left nares were perceptibly larger.

The left half of the abdomen and the left labial fold were distinctly fuller. Palpation in the median line near the umbilicus showed *diastasis recti*, admitting the finger tips.

No areas of cutaneous congestion or deviations with regard to hair distribution were noted in the examination of the skin.

A tabulation of the significant measurements follows. These include comparative measurements of the bones, made directly from the Roentgen ray film.

Items.		Right.	Left.
Height	83 cm.		
Weight	14 kg.		
Cephalic girth	47 cm.		
" breadth	13 cm.		
" length	14.5 cm.		
Length of leg	39.6 cm.	41.2 cm.
" femur (Roentgen ray)	20	21
" tibia "	16	16.5
" fibula "	15	15.7
Thigh girth	29	32
Calf girth	21	22.2
Length of arm	37.5	40
" humerus (Roentgen ray)	13.2	15.2
" radius "	11.2	11.5
Biceps girth	18	19
Hand girth	14	15
Length of foot	12.4	13.4
Width of foot	4.5	5.1
Length of ear	5.7	6
Width of palpebral fissure	0.8	1
Carpus Ossification Areas:			
Magnum	7 x 8 mm.	5 x 7 mm.
Unciform	6 x 8	5 x 8
Cuneiform	4 x 5	3 x 4
Semilunar	3 x 3	absent

Mental Development. A careful mental examination was made of this child when she was two and a quarter years of age and again when she was three years and four years of age. Her mental development has shown consistent retardation, though not on so low a level as the preceding case, S. D. The subnormality, however, justifies a diagnosis of mental defect of high grade.

On the first examination her chronologic age was two and a quarter years, her developmental level approximately eighteen months. At the chronologic age of three years her developmental level had reached two years. At the chronologic age of four it had reached approximately two and a half years. At each developmental examination, therefore, the developmental quotient (comparable to the I. Q.) was between sixty and sixty-five.

If, therefore, we plot the curve of mental growth diagrammatically as for the case of S. D., we obtain a similar picture of constancy in the subnormal rate of development. The accompanying psychograph (Fig. 6) summarizes the findings of the developmental examination. The developmental-age ratings were based on determinations of motor capacity, language, adaptive behavior and personal-social behavior, in accordance with the diagnostic procedures used at the Yale Psycho-Clinic in the examination of pre-school children.

Hemihypertrophic Cases Reported in Literature to Date. Total Number 53. Although hemihypertrophy has been reported in the

medical literature of various countries for over a half century, a careful canvass of this literature netted a total of only 53 cases, including one kindly communicated to me by Dr. C. T. J. Dodge prior to publication. Thirteen of these cases have accrued since my previous tabulation made in 1921. I have merged all of these cases into one table, which is reproduced herewith.

The total figures show a slight preference for the female sex and for involvement of the right side. Eight cases or over 15 per cent are associated with mental subnormality. Almost half of the cases showed complicating skin lesions.

It is evident that hemihypertrophy is by no means an altogether benign anomaly, that it represents a disturbing deviation of the

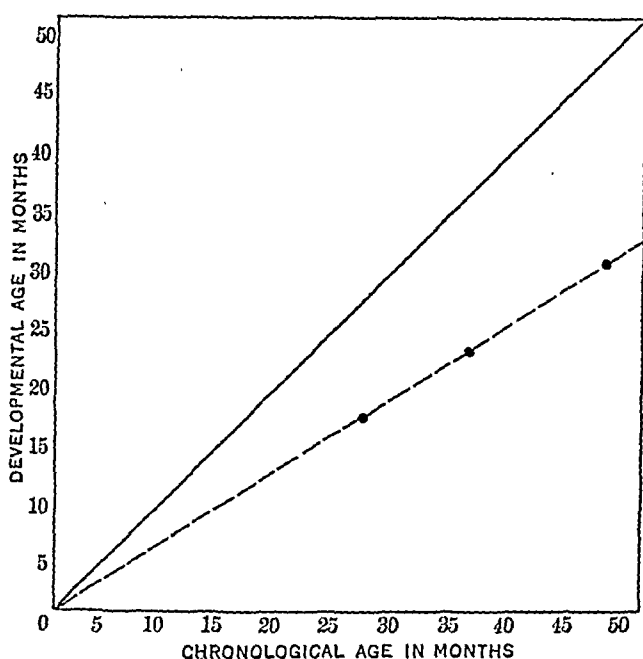


FIG. 6.—Mental-growth chart of CASE II (M. S.). The solid line shows the diagrammatic normal curve of growth. The broken line represents approximately the retarded course of growth of M. S., as shown by developmental-age ratings made when she was two years and three months, three years, and four years of age.

normal developmental complex. The nature of this disturbance may be considered by an analysis of what is known regarding the process of twinning.

Hemihypertrophy as a Phase of Twinning. Although considerable obscurity must attach to the origin of hemihypertrophy, the mode of its genesis may be eventually clarified by the researches of experimental biology. Many of these researches naturally bear on problems of symmetry, dichotomy, and growth regulation.

In earlier papers, we have suggested that human hemihypertrophy can be conceived as an imbalance of the normal process of twinning which underlies all bilateral structures. From this point of view,

Author.	Sex.	Age.	Side.	Mentality.	Skin complications.	Special features.
Bousquet, M. Pierre, 1921 .	F.	4 mos.	R	Undetermined	None	Lateral deviation of right phalanges.
Hall, Geo. E., 1921 . . .	F.	7 mos.	R	Without a blemish	Lips, ear, tongue, cheek asymmetrical. Nipples, mammae, scapula and clavicles equal. Cranium symmetrical. May involve only soft parts. May be false type.
Babouneix et Buizard, 1922	M.	4½ mos.	R	Very extensive nevi particularly of left leg	Marked transverse nasal vein.
Vonderweidt, Dr., 1922 .	M.	11½ mos.	R	(Dentition delayed)	Right side more congested when infant cries	Asymmetry more pronounced in lower extremities.
Cozzolino, O., 1923 . . .	M.	6½ mos.	L	None—clear	Skull symmetrical.
Paterson and Reynolds, 1923	F.	6 mos.	L	Seemed normal	Involves face only, right permanent, upper molar enlarged and left missing.
Paterson and Reynolds, 1923	F.	13 yrs.	R	Right breast larger—more pendulous.
Reed, A. C., 1923 . . .	F.	15½ yrs.	R	Normal, bright demeanor	Diffuse areas of passive congestion mostly on right leg, thigh buttocks and lumbar region	Asymmetry of tongue caused difficulty in <i>th</i> sound and in swallowing.
Stanton, J. N. and Tuft, Louis, 1923	F.	16 yrs.	L	Normal	Negative	Tongue, lip, and right pupil all larger on right side.
Lisser, Hans, 1924 . . .	F.	45 yrs.	R	Nervous, depressed	Finger nails, right hand dry, rough, ridged (left, smooth, glistening). Mustacho fuller on right side, hair coarse, dry.	Macrodactyly. Deformity of left knee. Varicose veins.
Mohr, Geo. J., 1925 . . .	F.	9 mos.	L	Retarded; unable to sit alone	Clear, dry	Left side relatively immobile in smiling.
Dodge, C. T. J., unpublished, 1926	M.	3½ yrs.	R	Mentally subnormal	A museum of nevi lipomata	Varied (see table).
Gezell, A., (present publication), 1926	F.	18 mos.	L	Mentally subnormal	None	
Gezell, A. Totals of 40 previous cases, tabulated in 1921, Arch. Neur. and Psychiatry, vol. vi, pp. 400	19 M. 21 F.	13 L. 27 R.	5 cases mentally subnormal	19 cases with skin complications	
Grand total	{ 23 M. 30 F. }	{ 35 R. 28 L. }	{ 8 mentally subnormal. 25 L. }	24 cases with skin complications	

hemihypertrophy is an epigenetic deviation rather than a germinal deformity. It represents some defect of the inner organismic regulation, or some disparity in the intimate environmental factors exerted in the early stages of cleavage. It is, accordingly, not an altogether unique anomaly but may be brought into the category of twinning and of double monstrosity.

Bateson has given us a very broad conception of twinning in his formula "the production of equivalent structures by division." He regards it as a fundamental manifestation of life. "When I look at a dividing cell, I feel as an astronomer might do if he beheld the formation of a double star; that an original act of Nature was taking place before me." Cellular division, as such, is not twinning; but the tendency of the divided or repeated parts to assume symmetrical relations may be so regarded; and this tendency is an almost universal feature of biologic mechanics. The fact that the experimental embryologist can bring about the growth of a paired structure by a simple wound of a single limb bud reveals the fundamental nature of twinning. Of similar significance is the fact that Loeb produced a 90 per cent increase in twins by a simple immersion of his experimental eggs in lime-free sea water, which caused the segments of the living eggs to fall apart as they were formed. Newman, likewise, regards the phenomenon of twinning as a "very fundamental process almost universal in the field of biology. For wherever we have bilateral doubling, we have twinning in some form."

From this point of view every bilateral individual may almost be considered as being morphologically a pair of twins. This view is so legitimate that it need not be called paradoxical. The human individual is undoubtedly derived from a single fertilized cell. He is monozygotic in origin. From this zygote, through a process of symmetrical division, develop all his right and left hand homologous organs and the right and left halves of his "unpaired" organs and structures. He is a product of developmental duplicity. Now in the case of true, complete monozygotic twins, this process of duplication has been carried to such a degree that two offspring result from the single ovum. A perfectly symmetrical bilateral individual on the one hand, and a perfect pair of duplicated individuals on the other represent the ideal extremes of the process of twinning. Between these extremes there are many gradations and deviations, some of them benign others monstrous, in character. Instead of a full twinning of the whole body, there may be twinning of various parts or only of one part. For example in the type of twinship known as *diprosopus diophthalmus*, described by Ballantyne, "the size of the head and the presence of two noses may be almost the only signs of duplicity."

The studies of Stockard and of Wilder have concretely shown the close genetic relationships between monozygotic twinning and double monstrosity. Stockard has also experimentally produced in the

trout and in the sea minnow unilateral deformities of development which resembled hemihypertrophy. He was able to arrange specimens of his experimental fish in graded series, demonstrating "a continuity of the series from *monstra in defectu* through the simple normal individuals to *monstra in excessu* and finally identical twins."

Stockard holds that the specific rate of development in any animal is probably dependent upon the rate of oxidation in the protoplasm of the species. Experimentally, therefore, the rate of development may be retarded by lowering the surrounding temperature, which reduces the rate of oxidation. Stockard found that "practically any deformity recorded in the literature other than those resulting from germinal variations or mutations may be induced by lowering the temperature and thus modifying the developmental rate."

The exact manner in which these developmental deviations are accomplished, is differently interpreted by different biologists. The tendency of recent research is to stress not the inherent molecular constitution of the germ, but the reaction of the specific growing protoplasm to the immediate environmental conditions. R. S. Lillie has suggested that the process of development is basically regulated by some physiologic influence of a repressive or inhibitory kind comparable to chemical-distance-action, which is indeed essentially a form of bioelectric control through potential difference. C. N. Child has elaborated the concept of the physiologic gradient.

This concept affords some clue to the mechanism of hemihypertrophy, or at least to its rationalization. Child asserts that at present there is "no evidence to indicate that axiate pattern can arise in any other way than as a gradient in a physiologic state." Polarity and symmetry therefore are dependent primarily upon "quantitative dynamic gradients in living protoplasms," whose existence Child has experimentally demonstrated in numerous ways. Accordingly, "physiologic dominance" and "physiologic isolation," and the relations between them are the dynamic factors which determine form regulation, symmetry, and frequently duplication and reduplication. Or one dominant region, because of its shape, may split into two regions of physiologic dominance, which will result in a greater or less degree of twinning. The range of dominance also plays a role in determining the limit of individual size. Since the concepts of gradient, dominancy, and isolation are essentially quantitative, it follows that a slight quantitative imbalance in the early stages of embryonic cleavage, might project itself into the whole-growth cycle as either a partial, or a total unilateral asymmetry.

Although one speaks of total hemihypertrophy as though it were a defined clinical entity it should be emphasized that even among the relatively small number of cases recorded in the literature, there is an impressive range of variation. One case will show a few nevi, another extensive nevi, another will report the skin to be entirely normal. In some cases the vascular complications are conspicuous,

in others wanting. The fact that hemihypertrophy is associated with both normal and defective mentality also is noteworthy.

Does not this variability in associated symptoms suggest that the condition arises out of environmental or epigenetic conditions? Growth is constantly regulated by interacting factors, and the specific structural features of any given case of hemihypertrophy will depend upon the precise moment at which the disturbing influence began to operate. The severity of the cerebral arrest, for example, will depend upon the dominance or the developmental stage of the neurogenic portions of the embryo. We are thinking here of subtle inhibitions or arrests of growth in the morphogenetic interplay of various organ systems, or even in the several components of a complicated system like the cerebrum. If grosser teratologic suppressions occur, subtler alterations are theoretically even more certain. On the grosser scale, Stockard, for example, found that the initial growth which gives origin to an embryonic system such as the brain and spinal cord "is linear in type, until a definite length is attained when linear growth subsides. This is followed by a series of lateral outgrowths in consecutive fashion. These lateral outgrowths from the central nervous system may be experimentally suppressed by slowing development at definite times . . ." The constantly changing status of the embryonic organs and the sensitiveness of the dynamic equilibrium which prevails furnish an ample basis for variable peculiarities in the pathologic picture of hemihypertrophy.

There can be little doubt that in some instances there is more than a morphologic difference between the opposite sides of the body. There is a perceptible physiologic or energetic difference, which heightens the temperature of the affected side, accelerates the growth of the nails and hair, and even hastens the eruption of the teeth on that side. Thus in one instance the developmental disparity was so great that there were eight teeth on the hypertrophic side with none erupted on the normal side.

This amazing discrepancy obliges us to recognize an energetic difference. It means that sometimes an individual may have two physiologic ages at the same time, one for each half of a developmentally asymmetric body. It also suggests that in some of these cases the physical signs of senility might be detected earlier on one side than on the other. This is another striking indication of the twoness of the hemihypertrophic individual.

Wilder has studied the genetic relationships between monozygotic twinning and double monsters (diplopagi). A gradation of the interrelations of various sorts of diplopagi and duplicate twins is diagrammatically pictured in the accompanying figure (Fig. 7). This diagram does not exhaust all of the possibilities, and does not aim to include those instances where one twin is included by the other, or where one twin becomes a mere parasite upon its normal co-twin. Incidentally, it may be recalled that such a parasite may degenerate

into an acephalic, acardiac, trunkless or amorphous mass. Here, as Ballantyne remarks, Nature "attains to the extreme limit of teratologic expression."

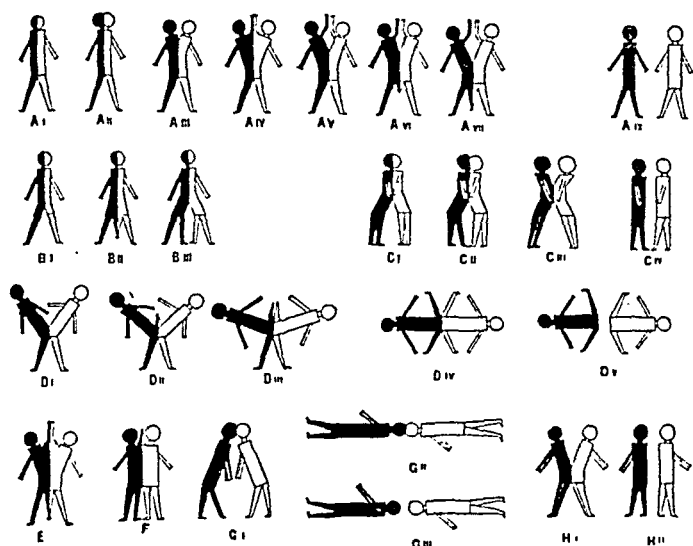


FIG. 7.—Wilder's diagrams showing the interrelations of various sorts of diplopagi and duplicate twins. (From *American Journal of Anatomy*, 3, 473.)

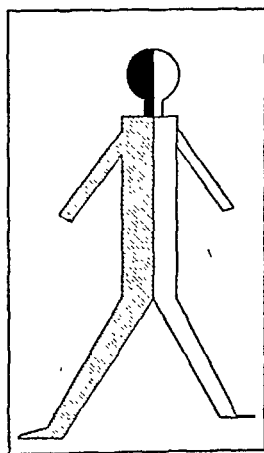


FIG. 8.—Diagram suggesting hemihypertrophy as a variant between AI and AII in the above series. (Fig. 7.)

Twinning, therefore, is a highly variable process which expresses itself on an enormously wide gamut. It may produce perfect symmetry and mirror imagery; or it may produce gross disparity. Nowhere in the study of man do we find such complete duplication

of individuality as among monozygotic twins; and nowhere do we find also such profound and monstrous degrees of individual difference as among twins derived from the selfsame egg. By the same token we may expect to find mild degrees of monstrosity or of incipient monstrosity such as hemihypertrophy embodies. We might then add to Wilder's diagrams a silhouette of an individual whose morphologic eccentricity is indicated by a larger and a lesser half. (See Fig. 8.)

H. H. Newman has made extensive studies of twinning in the armadillo. This work formed the basis of his volume on *The Biology of Twins*. More recently he has made an experimental analysis of twinning in the Pacific Coast starfish, and written an additional volume entitled *The Physiology of Twinning*. This volume contains material of medical interest—a chapter on the developmental hazards of human twins, and a chapter on hemihypertrophy. In many respects Newman's interpretations are in harmony with those already referred to. He believes that "twinning is essentially a phenomenon involving a physiologic isolation of equivalent parts of the blastoderm." The cause of the isolation is a temporary cessation or retardation of development at a critical period.

In his discussion of hemihypertrophy he suggests that the condition may be "due to a physical inequality of the two bilateral primordia so that one side would be more affected by subnormal conditions than the other Even with this possible explanation of asymmetry in mind I find myself in essential agreement with Dr. Gesell in his interpretation of hemihypertrophy as a minimal phase of double monstrosity. We may conclude that, since twinning in general consists of a more or less complete isolation, physiologic at first and later physical, of the bilateral primordia of a single embryonic axis, there may readily occur slight degrees of physiologic isolation or independence of the two halves of the body. Hemihypertrophy, complete and incomplete, would then be the result of some deficiency confined to one side, and the associated peculiarities would be viewed as secondary consequences of the primary deficiency."

One of these possible secondary consequences is mental defect. Although it is not an inevitable consequence it is sufficiently frequent to be significant. It suggests that an abnormality in the process of bilateral doubling may involve important disturbances of normal tissue development of the individual. Total hemihypertrophy, itself, is a rare phenomenon; but there may well be numerous instances of concealed or unrecognized asymmetry which bear a comparable relation to the production of mental deficiency. Probably a considerable proportion of congenital cases of mental deficiency may be attributed to epigenetic factors similar to those discussed in connection with hemihypertrophy. It is in this sense

that the study of twinning reveals new fields for the discovery of the causes of developmental defect.

Summary. 1. The medical literature on hemihypertrophy is reviewed and brought to date. Forty cases of the total unilateral type were tabulated by the author in 1921. Since then 13 additional cases have accrued. Of the combined number of 53 cases, 23 are male, 30 female. The right side was affected in 35, the left in 28. Skin complications were present in 24 instances. Mental subnormality was found in 8 instances.

2. The author reports a second case associated with mental defect. The subject is a girl examined at two, three and four years of age. The mental and physical measurements indicate that the condition has remained relatively constant. Remeasurements of the author's earlier case showed the same constancy in both its mental and physical features.

3. Hemihypertrophy is interpreted as a minimal form of twinning. Its genetic relation to the normal process of bilateral doubling and of double monstrosity is indicated. Recent researches in the field of experimental biology are cited, notably those of Stockard, Wilder and Newman.

4. The significance of the physiologic gradient, of physiologic isolation and of the partial retardation of developmental rate is considered in the pathogenesis of hemihypertrophy.

5. The relatively high incidence of mental defect is considered significant. The proportion of mentally subnormal cases would probably be still higher if mental examinations had been made and if some of the subjects had been more advanced in age. The mental defect is attributed to a disturbance of normal tissue development associated with an imbalance of the embryonic process of twinning.

6. Deviations or imperfections in twinning may play a very influential role in the production of developmental defect, though the details of the mechanism are not understood. Further biometric and clinical studies in asymmetry are therefore of medical importance.

The bibliography below is supplementary to a more extended one published in 1921 with the author's article in *Archives of Neurology and Psychiatry* (vol. 6).

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THE ELECTROCARDIOGRAM IN BRONCHIAL ASTHMA.

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THE compensatory capacity of muscular structures in the body is biologically interesting. The response of the muscle cavities to obstacles to their proper contraction is particularly exemplified by hypertrophy of the musculature of the left ventricle of the heart in hypertension.

In the present study, we analyze the electrocardiograms of a series of cases in an endeavor to ascertain the effects of chronic emphysema and bronchial asthma upon the right ventricle.

The Electrocardiogram in Cardiac Hypertrophy.—It is important to distinguish the mass of right heart musculature from that of the left ventricle. Thus there are two main divisions of the mass of heart muscle tissue: (1) The vortex fibers arising along the entire

circumference of the coronary sulcus and spreading over the entire surface of both ventricles to turn in at the apex and form the inner layer of muscle of the left ventricle; (2) the main mass of muscle of the wall of the right ventricle.¹ This anatomic distinction implies also a physiologic one for each of the heart chambers.

It has been shown by Einthoven,² Müller,³ Lewis and Gilder,⁴ and others⁵ that certain clinical valvular conditions cause more or less typical changes in the electrocardiogram corresponding to the preponderating hypertrophy of one or the other chamber of the heart. Although there may be other factors influencing the form of the electrocardiogram,⁶ preponderance of one or the other ventricle shown in the electrocardiogram may be taken as an index of relative hypertrophy.

The normal *Q-R-S* group is produced by the algebraic summation of the left ventricular electrocardiogram (levocardiogram) and the right ventricular electrocardiogram (dextrocardiogram). In the normal electrocardiogram, the effects of the two ventricles, in spite of the greater mass of the left, are fairly well balanced, producing the normal *Q-R-S* curve. A relative increase in the mass of the one or the other chamber alters the balance between right and left ventricular effects.

When the heart is greatly hypertrophied, preponderance of one side or the other is the main factor influencing the ventricular complex of the electrocardiogram. Variations in the position of the heart is another important factor. It has been shown that the relative dilatation of the two chambers, on the contrary, plays no appreciable part in determining the form of the ventricular complex. Prominent Q_3 and S_1 in the electrocardiogram are right ventricular effects. R_3 is chiefly a right ventricular effect. The tall R_3 and deep S_1 of right ventricular hypertrophy are the expression of preponderance of the dextrocardiogram.

Lewis concluded that the physical signs which are customarily employed at the bedside to differentiate left from right ventricular hypertrophy have little or no real value as checked by postmortem observations. In studying hypertrophy, even inspection of the exposed heart is quite insufficient, and a method of weighing the muscles of the separate chambers is alone reliable.⁴

The electrocardiographic curves, on the contrary, appeared in harmony with our knowledge of hypertrophy in various forms of valvular conditions. The view that hypertrophy is secondary to increased work, and that such hypertrophy is manifested by those heart chambers upon which the increased burden falls, is paramount today. The theory finds full support in clinical observations upon mitral stenosis. High blood pressure and aortic disease appear to be especially potent in creating a preponderance of the left ventricle. The commonest type of hypertrophy, however, is a uniform hypertrophy. In renal disease this is the rule.

The characteristics of the electrocardiogram have not been previously investigated in relation to bronchial asthma.

The Pulmonary Circulation and the Heart. It has long been recognized that a mechanical relationship exists between the pulmonary circulation and the condition of the right side of the heart. Clinically, it is known that prolonged pulmonary stasis and increased pressure in the pulmonary circulation result in right heart enlargement. In mitral stenosis or where pulmonary resistance increases, the initial tension of the right ventricle increases with the pressure in the pulmonary vessels; hypertrophy then follows. This sequence of events is rational and easily understood. In cases of hypertension, there is often hypertrophy of both the left and right ventricles. This is because the right side acts as an auxiliary pump to maintain a greater initial tension in the left ventricle.

In cases of destruction of part of the lung tissue such as takes place in pulmonary tuberculosis, there develops a compensatory dilatation of other capillaries. This accounts for the observation that right ventricular predominance is not found more frequently in association with fibroid phthisis, or with pleural adhesion than with other types of pulmonary fibrosis.⁷ The same holds true when, experimentally, one or more of the pulmonary veins are tied off.⁸ In these cases, it is found that there is none or only very slight increase of pressure in the remaining pulmonary veins, due of course to compensatory dilatation of the remaining vascular field. Clinically, the interesting observation may be made that the pulmonic second sound does not become accentuated in cases of postoperative pulmonary embolism, and I have observed it in a number of cases. This indicates that there is no increase of pressure in the pulmonary artery after pulmonary embolism, due to the compensatory dilatation of the nonoccluded vessels.

The effect that this compensatory process will have on the right ventricle varies with the extent of the narrowing of the stream bed of the lungs. At first, the dilatation of the arterioles will offset the narrowed blood bed, but with more extensive obstruction of the pulmonary vessels, the right ventricle will be called on for more work to maintain the minute volume flow in the lungs, and will dilate and eventually hypertrophy. This has been shown experimentally.⁹

Respiration and Pulmonary Circulation. With each inspiratory spreading of the chest, in normal respiration, the negative intrathoracic pressure increases. All the tissues in the thorax come into a state of elastic tension, the walls of the heart and the great vessels partaking in this. Inspiration, therefore, produces suction of blood from the periphery into the large veins and into the right heart. The pressure in the pulmonary capillaries increases as the air vesicles distend with inspiration, forcing the blood through the pulmonary veins into the left heart.

In asthma, the defective respiration is characterized especially

by expiratory dyspnea, producing increased intravesicular tension in the lung. This is the prominent functional factor in the production of pulmonary emphysema. Most asthmatics, therefore, develop emphysema to a decided degree. Again, the expiratory dyspnea and increased intravesicular tension of air in the lungs have a direct effect upon increasing the blood pressure in the pulmonary artery and thus can be assumed to have an effect on the right heart. That is, the strain upon the heart is probably largely due to increase of pressure in the pulmonary circuit during forced expiration.¹⁰

A lesser factor tending to produce right heart hypertrophy is the nasal obstruction occasionally present in cases of bronchial asthma.¹¹

Studies on patients suffering from chronic emphysema and bronchial asthma showed that the total lung volume remains about the same, but the vital capacity is much diminished and the residual air very much increased, indicating a compressed and narrowed capillary field in the lungs.¹²

Emphysema and Cardiac Hypertrophy. — Emphysema accompanies long-standing asthma. With that, of course, pathologically there is marked thinning of the vesicular walls and consequent narrowing of the vessels and capillaries. Occasionally, these become occluded and even torn through.¹³ This series of events tends to occur in most cases of bronchial asthma—in the long standing and intractable cases more than in those of short duration. The capillary field is thus lessened without the possibility of a compensatory dilatation. As a result there is dilatation and atherosclerosis of the pulmonary artery and dilatation and hypertrophy of the right ventricle, as it is called upon to force the same amount of blood as before through the narrowed capillary field of the entire lung. Finally this may even lead to cardiac insufficiency.

Clinical Comments. The clinical recognition of right ventricular hypertrophy in bronchial asthma is not emphasized in most studies of the subject. With reference to emphysema, von Leube states in the differentiation from cardiac asthma that a "dilatation affecting essentially only the right heart points to a spasmodic asthma."¹⁴

As noted above, the experimental method of occluding the pulmonary circulation or increasing the pulmonary resistance in other ways thereby to produce effects on the heart, is not helpful in the study of bronchial asthma.

The marked encroachment of the lung volume upon its capillary capacity together with the varying intrathoracic pressure constitutes a decided strain upon the right ventricle, to which the organ responds by hypertrophy. Enlargement of the right heart is usually found in advanced emphysema, unless masked by the physical signs of the emphysematous lung.

The analysis of Roentgen ray and electrocardiographic findings in pronounced cases of bronchial asthma of long duration is of

assistance in diagnosis. We have not included roentgenographic analyses in this study. The electrocardiogram is especially helpful in showing the relative preponderance of one side of the heart over the other.

The association of complicating clinical features such as arterial hypertension producing left ventricular preponderance makes it important to analyze the cases in detail. The record of the blood pressure is one important index and the amount of emphysema is, of course, the other. The cases are tabulated to show these and other relevant clinical findings such as duration of the disease and severity of the attacks. The duration and severity I have grouped together as we aim to discover the summation of the effects of asthma. The cases are also classified in groups according to age and the diastolic blood-pressure findings. I consider the diastolic reading, as it is more constant, more important than the systolic in the analysis of blood-pressure studies.

Analysis of Electrocardiographic Records. The electrocardiograms were reported in the usual routine manner with an endeavor to commit ourselves to an opinion of right preponderance when such a tendency was indicated by a combination of deep S_1 with low R_3 , or with prominent Q_3 . On the other hand, left preponderance was indicated by deep S_3 and high R_1 .

Four predominating characteristics were found in the analysis of the electrocardiograms of these cases: (1) Left ventricular preponderance; (2) right ventricular preponderance; (3) high P (auricular) wave in Leads II and III; (5) T wave inverted in Lead III.

Other conditions being equal, left ventricular preponderance is an almost constant association of high blood pressure (Table I).

TABLE I.—CLASSIFICATION OF ELECTROCARDIOGRAPHIC CHANGES ACCORDING TO DIASTOLIC BLOOD PRESSURE.

Diastolic blood-pressure.	No. cases.	No pre- ponderance.		R. V. P.		L. V. P.		T _a inverted.	
		No.	%.	No.	%.	No.	%.	No.	%.
Under 70 mm. Hg	9	4	44	4	44	1	11	2	22
70 to 79 mm. Hg	14	7	50	2	14	5	35	3	21
80 to 89 mm. Hg	11	6	54	1	9	4	36	2	18
90 to 99 mm. Hg	8	1	12	2	25	5	62	2	25
100 and over mm. Hg . . .	8	1	12	1	12	6	75	1	25
Totals	50	19		10		21		10	

When in a case of hypertension, therefore, there is no ventricular preponderance, we may assume the coexistence of right heart hypertrophy. In cases of emphysema and asthma, we must assume this

on the basis of pulmonary stasis. Of the 21 cases of left ventricular preponderance, the largest number showed hypertension. It is seen that the higher the diastolic pressure, the greater is the proportion of cases showing left ventricular preponderance. It is noted that in a number of our cases, even with high blood pressure, there is no left ventricular preponderance. That is, the normal balance between the musculature of the two ventricles is maintained. This implies and indicates right ventricular hypertrophy. The majority of cases showing left ventricular preponderance are above the age of forty years or with a diastolic pressure above 90 (Table II).

TABLE II.—CLASSIFICATION OF ELECTROCARDIOGRAPHIC CHANGES ACCORDING TO AGE.

Age.	Number.	No preponderance.	R. V. P.	L. V. P.	T ₂ inverted.	P ₂ and P ₄ high.
Under 20	6	3	3	0	1	1
20 to 29	9	4	4	1	1	2
30 to 39	6	4	1	2	1	
40 to 49	18	6	1	10	4	
50 and over	11	2	1	8	3	1

Thus it is evident that the superposition of the effect of left ventricular preponderance on a preëxisting right ventricular preponderance masks the hypertrophy of the right ventricle in these cases of asthma. It is probable and it may be assumed that a certain amount of right ventricular hypertrophy is masked by the predominating hypertrophy of the left ventricle.

It is seen from the table that of the 50 cases 10 showed right ventricular preponderance. This does not present the full number in which right hypertrophy took place. Although not tabulated, in this group may properly be included the cases showing no preponderance but showing hypertension or some other factor which counterbalanced the effect of asthma. It becomes apparent that the electrocardiogram must be considered in conjunction with all the other clinical aspects of cases in order that it may be correctly interpreted.

The frequent association of the high *P* wave with right ventricular preponderance suggests that this is another evidence of the effect of pulmonary stasis on the right heart. Since the effect is first upon the ventricle and only secondarily upon the auricles, a high *P* wave would theoretically not be found in association with left ventricular preponderance except in cases of mitral stenosis. This assumption is supported by the analysis of our tables. It is a surprising finding that the 4 cases showing a high *P* wave in Leads II and III occur in cases in which there is right ventricular preponderance (Table III).

TABLE III.—RELATION OF HIGH P WAVE IN LEADS II AND III TO VENTRICULAR PREPONDERANCE.

Name.	Sex.	Age.	Diastolic pressure.	Preponderance.
I. F.	M.	26	60	R. V. P.
L. G.	F.	21	74	R. V. P.
A. E.	F.	50	94	R. V. P.
M. L.	M.	11	Low	R. V. P.

The inversion of the *T* wave in Lead III showed no particular relation to the ventricular predominance (Table IV). Three of the inverted *T*₃ electrocardiograms showed no predominance;

TABLE IV.—RELATION OF INVERSION OF THE T WAVE IN LEAD III TO VENTRICULAR PREPONDERANCE AND SYSTOLIC PRESSURE.

	Number of cases.	Systolic pressures.
<i>T</i> ₃ inverted with no ventricular preponderance . . .	3	124 100 114
<i>T</i> ₃ inverted with right ventricular preponderance . .	3	96 146 137
<i>T</i> ₃ inverted with left ventricular preponderance . .	4	114 100 140
Total <i>T</i> ₃ inversion cases	10	

TABLE V.—RELATION OF RIGHT VENTRICULAR PREPONDERANCE TO AGE AND BLOOD PRESSURE.

Name.	Sex.	Age.	Systolic pressure.	Diastolic pressure.
A. E.	F.	50	160	94
I. F.	M.	26	96	60
B. F.	F.	40	137	78
L. G.	F.	21	100	74
F. K.	F.	37	122	88
M. L.	M.	11	90	
M. M.	M.	12	90	
W. M.	M.	7	96	64
M. R.	F.	23	128	98
E. S.	F.	29	146	106

three showed right predominance and four showed left ventricular predominance. It is usually held that the inversion of the *T* wave bears a relation to hypertension. It does not seem to be the case in this group. As noticed from the table, the blood pressures are at various levels in these cases. Although *T*₃ inversion has no apparent relation to the blood pressure, it occurs in cases above the age of forty years, which suggests that it may be an evidence of myocardial changes associated with advancing age.

Conclusions. 1. Of 50 cases of bronchial asthma and emphysema, 10 (20 per cent) showed electrocardiographic evidence of right ventricular preponderance.

2. The remaining cases showed electrocardiographically no preponderance and left ventricular preponderance in about equal number. Among these, a large proportion of cases showed hypertension and aortic atheroma; factors which influenced the hypertrophy of the left ventricle to a degree sufficient to mask the electrocardiographic evidence of right ventricular hypertrophy.

3. Four of the cases showing right ventricular preponderance also showed high P_2 and P_3 .

4. Inversion of the T wave in Lead III showed no particular relation to the ventricular predominance.

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FACTORS OF A GROWTH REGULATORY NATURE IN TISSUE CELLS.*

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THE tissue culture method has rendered it possible to undertake accurate analyses of the cell nutrition and the interaction of the different cell types. It is possible to cultivate pure strains of cells with a known activity in a culture medium of invariable composition over long periods of time.

It is known from the investigation of Carrel that the growth of tissue cells is dependent upon the concentration in the pericellular

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fluid of substances from which the cells are able to synthesize their own cytoplasm, and of certain hormones. The growth-promoting substances, products of embryonic tissues and leukocytes, as taken up by the cells from the humors of the body, have been termed "trephones" by Carrel.

Experimental facts which shall be reported here lead us to assume the existence of certain growth principles besides the trephones, namely, those which circulate in the living protoplasm only. In other words, we are forced to conceive the existence of a hitherto disregarded circulatory system in the body, that is, a system, which probably is a kind of mutual exchange of protoplasm between the cells. These principles I have termed "desmones" (from *δεσμός*, a strap or string), and this name is used as a collective term for principles circulating in the protoplasm from cell to cell through the fine anastomoses, and mutually controlling the growth and proliferation of tissue cells.

Some years ago I reported experiments which showed that single isolated tissue cells *in vitro* were not able to divide and regenerate to form a cell colony. The cells lived and moved about, but were incapable of multiplying. When a certain number of cells were in protoplasmic interconnection, however, they were able to multiply.

It is well known that the intercellular connections of the tissue cells serve as pathways for the conveyance of stimuli of various kinds. When two pieces of pulsating heart were brought close together *in vitro*, the two pieces pulsating in different rhythms, I found that it was possible to obtain a physiological unit, a simultaneous contraction of the two pieces, when the contractile elements of the one piece of heart grew in protoplasmic contact with that of the other piece. A simultaneous contraction of the two pieces did not take place when a layer of fibroblasts was interposed between the two bits of heart; nor was simultaneous contraction obtained when the two pieces of heart belonged to two different species (duck and chicken). These facts seem to prove that the stimuli leading to contraction of the myoblasts are rather specific to species of cells and species of animal.

When cultivating tissue cells *in vitro* it will be found that for some reason or other the cells occasionally begin to grow badly and nearly die. Instead of a regular dense mass of tissue cells the culture is transformed so as to consist of cells arranged in irregular chains or in an open meshwork. It was evident that lack of trephones was not the cause of degeneration of the cells, because the culture medium contained plenty of freshly prepared embryonic tissue juice; nevertheless it was incapable of promoting the growth of fibroblasts. When a very minute piece of a fibroblast culture was brought in direct connection with the dying culture of cells a rejuvenation of the culture took place, that is, the degenerated fibroblasts now assumed the aspect of young cells in active condition

and began to proliferate vigorously. The rejuvenation of the cells directly opposite the added piece of fibroblast culture was very striking, even within a short time. The rejuvenation is probably due to the fact that a something is brought into the dying cells which hitherto has been missing.

When small quantities of leukocytes were added to a culture of dying fibroblasts this resulted also in a rejuvenation of the cells. It was observed that leukocytes form "provisional" anastomoses with the fibroblasts, and thus in this way may convey a something to the degenerated cells which causes rejuvenation.

When cultivating chicken sarcoma I have often noticed cultures that are growing badly. It has been possible to save cultures of almost dying sarcoma cells by adding pieces of normal growing cultures of fibroblasts. Even when cultures of the sarcoma cells looked hopeless, and only a few extremely degenerated cells were left, such cultures could be successfully rejuvenated by adding a piece of fibroblastic tissue.

As already mentioned, it was not possible to establish a physiological unit of two pieces of pulsating heart tissue belonging to two different species, nor was it possible to obtain a physiologic unit of two pulsating pieces of heart when a layer of fibroblasts was interposed. It was further observed that the growth of pure epithelium was not promoted by addition of fibroblastic tissue to it or *vice versa*, and an amalgamation of the two-cell types was not found to take place. The individual epithelial cells grew in solid contact with each other surrounded by fibroblasts. This fact shows also that the principles controlling the growth and multiplication of normal epithelium cannot be utilized by normal connective-tissue cells or *vice versa*. In contrast with the trephones, the desmones are specific.

If a few sarcoma cells are added to a culture of epithelium an amalgamation takes place immediately. A capital biologic difference between a normal and a malignant tissue cell is therefore this: The malignant cell is capable of utilizing the specific desmones, or growth principles, of all the various cell types in the organism, whereas an epithelial cell can utilize only the desmones of epithelial cells and fibroblasts only those of the fibroblasts. The explanation might, however, be that the malignant tissue cell is able to build up the growth principles, independent of the relation to other cell individuals.

We can summarize the result of our investigation by saying that the growth and proliferation of tissue cells depend upon the concentration in the pericellular fluid of certain food substances, the trephones of Carrel, and of hormones. Besides these external, non-specific growth principles we may now add certain internal, specific principles, the desmones, which rule coördinate growth of tissue cells and which are found to exist only in the living protoplasm of the cells.

We have learned from our experiments that the external growth principles alone are not sufficient to support the life and function of the tissue cells. Even under conditions where an abundance of trephones and hormones are to be found, isolated tissue cells are incapable of multiplying. How the phenomenon may be interpreted is not easy to say. We are justified in assuming from our experimental knowledge only the existence of such growth principles and correlation principles as mentioned.

Consideration of these principles seems to explain many physiologic cell processes.

The extent to which the desmones are specific we do not yet know; but there is every reason to believe that the healing of grafts mainly depends upon the possibilities of the grafted cells being in harmony with the cells of the host, that is, upon whether the grafted cells are capable of utilizing the desmones of the cells from the host or not. Even if the humors of the body are in no way antagonistic to the grafted cells, they will die if they are not able to accomplish an exchange of desmones.

The protoplasmic growth principles probably also play an important rôle with regard to processes of regeneration in the organism. The protoplasm of an organism may be recognized as a system. A dissolution of continuity develops the accumulation of growth principles in certain cells which causes multiplication until the connection is again established and proliferation ceases.

The malignant tissue cells behave in a quite different manner. These cells are characterized by this fact, namely, that they are not subject to the control of the organism as are the normal tissue cells. The malignant tumor cells may either be capable of utilizing the desmones of all cell types (heterotopic growth) or they are able to build up themselves the principles necessary for their growth independent of other cells. Single tumor cells are capable of multiplying in surroundings, where the same cells, had they been normal, could not have done so.

REVIEWS.

HUMAN PATHOLOGY: A TEXTBOOK. By HOWARD T. KARSNER, M.D., Professor of Pathology, School of Medicine, Western Reserve University, Cleveland, Ohio. Pp. 980; 463 illustrations, 20 in color. Philadelphia: J. B. Lippincott Company, 1926.

THE advent of a new textbook on a major medical subject, written by a recognized authority, is always a matter of importance to medical education and literature, and especially so in pathology where existing textbooks in English perhaps do not cover the field as thoroughly as is done in some other languages. With Dr. Karsner's known interest in "dynamic" pathology, it was to be expected that this phase would receive especial attention, and indeed he announces that his purpose is "to present the morphologic alterations incident to disease, in the light of modern views as to their functional significance."

How far has it been possible to realize this ambitious program within the limits of a single volume of less than a thousand pages? While agreeing with Dr. Flexner in his introduction, that the book provides a well-considered and successful compromise, we recognize certain items in which it falls short of one's desires. Thus rheumatic fever has had to be dismissed in less than half a page, and monsters just as summarily, the pathologic anatomy of all the anemias lumped with that of pernicious anemia, and the diaphragm apparently omitted entirely. Possibly these shortcomings, for which we sympathize with rather than criticize the author, can be overcome in another edition in which he is allowed more latitude. In many places, too, even the author's favorite—pathologic physiology—has had to be so reduced that the usual textbook treatment of morbid anatomy is approximated. On the other hand, the author points out that a textbook is only an introduction to the essentials of a subject, and he certainly has augmented this introduction with an extensive, up-to-date and well-chosen bibliography at the end of each chapter.

Presumably the high cost of printing has led the publishers so to reduce the margins that one experiences an uncomfortable sense of crowding; one might reasonably have asked for a less diagrammatic reproduction of many of the histologic illustrations. One notes "lymphocytes" (p. 205), "urinero" (p. 240), "cuxis" (p. 289), "Willins" (p. 444), "fenia" (p. 691), "compliment" and "mul-

itlocular" (p. 692), "rhachitis" (in index only), Fig. 195 is upside down, and a few similar errors, but on the whole the typography is excellent.

It will readily be seen that such details are unimportant or unavoidable with the limitations imposed. The style is clear and concise, and the statement authoritative, especially in those fields in which the author has worked personally, and these are by no means few. All who study this book must agree with the introducer that "the author has made a notable addition to the English literature on pathology."

E. K.

RECENT ADVANCES IN PHYSIOLOGY. By C. LOVATT EVANS, University College, London. Second edition. Pp. 366; 70 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, \$3.50.

WITH the exception of a slight addition to the chapter on Insulin, this edition is practically identical with its predecessor. It presents a brief, concise and fairly up-to-date account of a wide range of topics in physiology. The author devotes almost half the volume to blood and circulation. The remainder considers to some length tissue oxidation, the physiology of muscular contraction, the endocrines and certain reflex mechanisms. The book should be of value particularly as a general resumé of certain work too recent to have been included in the standard texts.

E. L.

ATLAS OF THE HISTORY OF MEDICINE: I. ANATOMY. By J. G. DE LINT, Lecturer on the History of Medicine, University of Leiden. Pp. 96; 199 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, \$6.00.

ANY reasonably intelligent member of our profession would like to know more about its history, if only he had more time or knew where to find the material, or had the price and so on *da capo*. Must we, then, follow the latest developments of the daily press and offer the material in picture form, easily and quickly assimilated and appealing to that childlike love of pictures which persists in most of us through life? If so, this atlas of anatomy should prove more efficient in arousing the historical curiosity of the average medico than more learned or wordy tomes, and, if for no other reason, is worth while. Singer's philosophic introduction also delivers a strong stimulus in its short two pages.

For confirmed followers of *Clio Medica*, this atlas, by the next president of the International Congress on Medical History, is also

desirable. Its two hundred illustrations and legends (biographic, bibliographic and illustrative of anatomic procedure) present for the first time, and in English, a pictorial history of this "basic discipline of all medical science" in convenient and useful form and include not a few illustrations that are difficult for the ordinary student to find elsewhere. The illustrations are well chosen and adequate, though some have suffered in the process of reproduction and are so compactly put together that much craning of the neck is necessitated. The atlas is a worthy supporter of the renewed interest that is being shown in the history of medicine, and it is hoped that the promised volumes of the panorama will soon be forthcoming. E. K.

OPHTHALMIC YEAR BOOK 1926. Edited by WILLIAM H. CRISP, Pp. 315; 9 illustrations. Chicago: Ophthalmic Publishing Company, 1926.

THE 1926 *Ophthalmic Year Book* (vol. 22) comprises thirty-two chapters with nine illustrations. It brings the literature up to date, by reviewing all the domestic and foreign magazines, not alone ophthalmic, but also general.

At the beginning of each chapter there is a bibliography covering the literature therein.

The classification of the abstracts, with each author's name and reference number at the beginning, makes this volume most useful for any one wishing to keep abreast of the literature. H. S.

PRACTICAL DIETETICS IN HEALTH AND DISEASE. By SANFORD BLUM, A.B., M.S., M.D., Head of Department of Pediatrics and Director of the Research Laboratory, San Francisco Polyclinic and Post-Graduate School. Second revised edition. Philadelphia: F. A. Davis Company, 1926. Price, \$4.00.

THIS book is a compendium of dietaries. Detailed lists of foods recommended, as well as those to be avoided, for almost all the ills known to man are set forth in good type. Clearness, simplicity in arrangement of subject matter and a good index commend the book to the busy reader. The rationale of the specific diets, however, receives little or no consideration, and the reader is left quite in the dark, usually, as to why one particular diet is preferable to another. Although its appeal is thus limited, the volume is useful as any encyclopedic presentation of facts may be. T. M.

THE ABDOMEN IN LABOR. By NORMAN PORRITT, M.R.C.S., L.R.C.P. (LOND.), Consulting Surgeon, Huddersfield Royal Infirmary. Pp. 73; 29 illustrations. London and New York: Humphrey Milford; Oxford University Press, American Branch, 1926. Price, \$1.75.

THIS rather curious little monograph on a sometimes neglected method of diagnosis in obstetrics represents the author's observations on many parturient women. A rather interesting essay by a general practitioner which won the Sir Charles Hastings Prize of the British Medical Association in 1926. P. W.

THE PATHOLOGY AND TREATMENT OF DIABETES MELLITUS. By GEORGE GRAHAM, M.A., M.D., F.R.C.P., Assistant Physician, St. Bartholomew's Hospital. Second edition. Pp. 230. New York: Oxford University Press, American Branch, 1926. Price, \$2.75.

THE second edition of this work embodies some of the important recent investigation in the fields of carbohydrate metabolism and the insulin treatment of diabetes mellitus. The physical, chemical and metabolic properties of insulin are discussed.

More emphasis is given to the importance of urinary sugar than is usual among American diabeticians. Again the alveolar air CO_2 determination, now seldom used in this country, is given a prominent place in the diagnosis, and in following the treatment in diabetic coma, while the CO_2 capacity of the plasma is dismissed with but the mention that "it is not so easily carried out as the estimation of the alveolar CO_2 ." Author and subject indices together with the bibliography appended to each chapter make the book a very practical starting point for study of the various phases of this subject. W. S.

THE PHYSIOLOGY OF THE CONTINUITY OF LIFE. By D. NOEL PATON, Regius Professor of Physiology, University of Glasgow. Pp. 226; 79 figures. London and New York: Macmillan & Co., Limited, 1926.

THIS book is the outcome of lectures given to classes of medical students. In it are assembled many recent observations and views on the processes going on in the various periods in the life history of the individual. These concern especially the leading factors in reproduction, growth and differentiation. Two interesting chapters are "The Influence of the Gonads upon the Soma" and "The Influence of the Soma upon the Gonads." In his effort to avoid accepting dogmatic statements, the author debates such questions

as spontaneous generation, the Mendelian laws of inheritance, chromosomes as carriers of hereditary characters and the transmission of acquired characters. By this method he hopes to arouse a more critical attitude in the minds of the students toward the unqualified statements in the textbooks.

W. A.

THE TREATMENT OF THE ACUTE ABDOMEN, OPERATIVE and POST-OPERATIVE. By ZACHARY COPE, B.A., M.D., M.S. (LOND.), F.R.C.S. (ENG.). Pp. 238; 146 illustrations. New York: Oxford University Press, American Branch, 1926, Price, \$3.50.

THE author states in his preface that this book is written primarily to help those doctors who are not much practised in abdominal surgery, but who may be called in an emergency to operate upon an acute abdominal condition. The book fulfills this requirement thoroughly, and, in fact, contributes much that can be of great value to men of vast experience in work of this kind. It should appeal also to that great group of young physicians, namely, the hospital intern and resident. So many of the simpler matters of technique are not brought out thoroughly and carefully in our large works that take up the subject in its wider scope. This little book may be considered in the light of a primer and a good one at that. In the vast majority of instances illustrations are well chosen and really show what they are intended to describe. The text presents the author's thoughts clearly and well, at the same time limiting the description to one method of treatment, the one that in the author's hands has given the best results. The book in this respect is unique and exceptionally valuable to the beginner because of its simplicity. The entire work is concerned merely with the treatment of the acute abdomen and does not touch upon the diagnosis. Were the reviewer to offer a criticism, it would be that one chapter be added on the diagnosis of the abdominal emergency.

E. E.

WHY INFECTIONS? By NICHOLAS KOPELOFF, New York State Psychiatric Institute. Pp. 182; no illustrations. New York City: Alfred A. Knopf, 1926.

THE first half of this book defines and describes the usual sites of focal infection. It seems a little too technical to hold the attention of its intended lay reader. The second half deals with the rôle of focal infection in generalized disease, stressing the difficulty of search and the uncertainty of result, once infected tissue is removed. Surgery is advised only when tissue has been repeatedly proved harmfully infected. The chapters dealing with mental disease and practical problems are especially praiseworthy.

C. L.

BOOKS RECEIVED.

- DeLamar Lectures, 1925-1926, of the School of Hygiene and Public Health, Johns Hopkins University.* Pp. 220; illustrated. Baltimore: Williams & Wilkins Company, 1926. Price, \$5.00. (To be reviewed later.)
- Early Days of the Presbyterian Hospital.* By D. BRYSON DELEVAN, M.D. Pp. 192; 34 illustrations. New York: Presbyterian Hospital in the City of New York, 1927. Price, \$1.50.
- Exophthalmic Goitre.* By JOHN EASON, M.D., F.R.C.P.E. Pp. 215; 34 illustrations. Edinburgh: Oliver and Boyd, 1927. Price, 12/6. (To be reviewed later.)
- Elements of Surgical Diagnosis.* By SIR ALFRED PEARCE GOULD. Sixth edition reviewed by ERIC PEARCE GOULD. Pp. 739; 20 illustrations. New York: Paul B. Hoeber, Inc., 1927. Price, \$5.00.
- Hewats' Examination of the Urine.* Revised by G. L. MALCOLM SMITH. Pp. 228. Seventh edition. New York: Paul B. Hoeber, Inc., 1927. Price, \$1.50.
- South America.* By FRANKLIN H. MARTIN, C.M.G., D.S.M., M.D., LL.D. Pp. 435; illustrated. New York and Chicago: Fleming H. Revell Company, 1927. (To be reviewed later.)
- Clinical Neurology for Practitioners of Medicine and Medical Students.* By EDWARD A. STRECKER, A.M., M.D., and MILTON K. MEYERS, B.S., LL.B., M.D. Pp. 410. Philadelphia: P. Blakiston's Son & Co., 1927. Price, \$3.50. (To be reviewed later.)
- This Business of Operations.* By JAMES RADLEY. Pp. 96. Cincinnati: The Digest Publishing Company, 1927.
- Textbook of Biological Chemistry.* By JAMES B. SUMNER, Ph.D. Pp. 283; 6 illustrations. New York: The Macmillan Company, 1927. Price, \$3.50. (To be reviewed later.)
- A Primer for Diabetic Patients.* By RUSSELL M. WILDER, M.D. Pp. 134. Third edition. Philadelphia: W. B. Saunders Company, 1927. Price, \$1.50. (To be reviewed later.)

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Gentian Violet and Acriviolet in the Treatment of Pernicious Anemia.

—H. MILTON CONNOR (*Med. J. and Record*, 1927, 125, 9) reports on the treatment of 18 patients with pernicious anemia by means of gentian violet and acriviolet alone or in combination. In every case, he has had a good result. The gentian violet is given in a solution of 1 to 1000 and 50 or more cubic centimeters of the solution are taken three times daily. The acriviolet has been used in only 4 cases. The dose of this has been 0.1 to 0.4 gr. in enteric capsules. He feels that the occurrence of such marked remissions as his report indicates and that the absence of recurrence in so many cases is more than a coincidence. However, he very conservatively states that his series is too small and the time too short since the inception of treatment to draw positive conclusions. Connor should, in a short time, have a large number of cases to report upon, as the number of patients who come to the Mayo Clinic suffering from pernicious anemia is very large.

Studies in Red Blood Cell Diameter. II. In Pernicious Anemia.

Before and during Marked Remission, and in Myelogenous Leukemia.

—In the second communication from the Boston group of hematologists, DONALD N. MEDEARIS and GEORGE R. MINOT (*J. Clin. Invest.*, 1927, 3, 541) make a report upon the diameter of the red blood cells during the remission of pernicious anemia. It has been found that during the spontaneous remission the diameter of the red cells becomes normal, as observed in 11 cases and even less than normal in 3 cases. This is an interesting observation and may help to mitigate the general use of this method of the study of the red cells. The authors also report upon the measurement of the red cells in 9 cases of chronic myelogenous leukemia and 2 cases of subacute aleukemic myelogenous leukemia. In these conditions the red cells were small in diameter, typical of the picture

that is seen in secondary anemia. In 1 of the cases of this type, however, there was a well-marked increase in the size of the cells during the latter part of the disease.

The Mechanism of the Action of the Hydrogen Ion upon the Cardiac Rhythm.—(*J. Clin. Invest.*, 1927, 3, 555) E. COWLES ANDRUS and EDWARD P. CARTER have previously reported that it is possible to control the rate of the sinus rhythm by changing the pH of the Locke perfusate. In the present study, effects of C_{H_2O} of the perfusing fluid have been studied, as well as the effect of increasing the carbonic content of the acid of the perfusate. They conclude that the changes in the rhythm of a dog's heart are not due to alteration in the ionization calcium and they show that increased carbonic acid content with perfusate without change in the pH increased the spontaneous development and the propagation of the excitatory process. They conclude from these studies that the difference in the hydrogen ion concentration within and without the cell is the factor controlling this excitation, as the cardiac tissue is particularly sensitive to alterations in the hydrogen ion concentration.

Digitalis and Diuretics in Heart Failure with Regular Rhythm, with Especial Reference to the Importance of Etiologic Classification of Heart Disease.—It has been the view of many cardiologists that digitalis affects very largely congestive heart failure when there is auricular fibrillation, but there is some divergence of opinion as to the value of the drug in heart failure with normal rhythm. Moreover, the etiology of the heart condition has not been considered in the response of the heart to digitalis. MARVIN (*J. Clin. Invest.*, 1927, 3, 521) has made a careful clinical study of the effects of digitalis alone and also in conjunction with diuretics. He shows in the results of his studies that digitalis in large doses in patients with advanced congestive heart failure and regular rhythm brings about consistent improvement in the group of heart cases which are designated as arteriosclerotic heart disease. It has some effect on the patient with syphilitic heart disease, but practically no effect in rheumatic heart disease. The same statement applies to the relief of edema by means of diuretic drugs after complete digitalization. Effective diuresis is accomplished in arteriosclerotic heart disease, whereas in rheumatic heart disease such is not the case. The author suggests that the difference of opinion that exists concerning digitalis in heart failure with normal rhythm may be the result of variations of the etiology of heart failure in the patients selected for treatment. He believes that if an etiologic diagnosis was made in each case, it would be possible to attain proper correlation of the results attained by various observers.

Auscultatory Percussion in the Diagnosis of Pleural Effusion.—Physical signs of disease of the thorax are for the most part standardized, and it is only occasionally that some observer of unusual clinical acumen develops or discovers some new sign which may be of value in the diagnosis of intrathoracic conditions. WEBB (*J. Am. Med. Assn.*, 1926, 88, 99) describes a method of auscultatory percussion in the diagnosis of pleural effusion, which promises to be of great value,

more particularly the differentiation of this disorder from a thickened pleura or advanced tuberculous lesions at the base of the lung. The method, in brief, is to note, when an effusion is present, a higher and shorter pitched note upon percussion of the spinous processes of the vertebræ with the bell of the stethoscope in the axilla.

SURGERY

UNDER THE CHARGE OF

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New Research in the Etiology of Cancer, with Reference to the Work of Gye.—SITTENFIELD (*Am. J. Roentgenol.*, 1926, 16, 525) asserts that the germ theory of cancer is not a new one. Often has it been advanced and as often been rejected. It has been pointed out that it does not explain cancer. This view was justified because no one had isolated an organism, which when injected into an animal would reproduce with certainty a new growth. Opponents of the germ theory are correct, if their contention rests purely upon the basis that the cancer question cannot be solved by setting up wholly an extrinsic bacterial origin. In this much Gye agrees that the extrinsic agent or virus by itself is incapable of producing malignant tumor formation. To do that it requires the coördination of the intrinsic factor or accessory substances produced by the cells themselves. The intrinsic factor or accessory substance varies from tissue to tissue and also from tumor to tumor. The outstanding feature of this new research is the supposition of the close association of this accessory factor with an infective agent. The physical and chemical properties of the so-called accessory factor are as yet not established, but possibly more knowledge of both agents may yield vital facts in the etiology of cancer, as, for instance, sex or age incidence, selective localization, the effect of chronic irritation and the relationship between benign and malignant tumors.

Undescended Testicle.—MEYER (*Surg., Gynec. and Obst.*, 1927, 44, 53) reports that the exact etiology of undescended and ectopic testicle has not yet been definitely settled. The histologic changes point to the fact that the spermatogenic cells are present and functionate in about 10 per cent of all cases. The interstitial cells which have to do with the development of secondary sexual characteristics are always abundantly present. Since these findings are almost constant, the undescended testicles should always be saved. Secondary complications occur. Malignant degeneration is not as frequent as is generally

supposed and fear of the same is no indication for orchidectomy. Chronic inflammation, the presence of a potential or real concomitant hernia, practically always present, torsion of the spermatic cord and strangulation of the testicle are occurrences so frequent that surgical interference is always indicated. The best time to operate is before puberty, between eight and ten years of age. Torek's method of orchipexy is the best means of curing the hernia and placing the testicle into its normal position. It is logical and surgical, maintaining full blood supply to the testicle which comes to lie in the bottom of a well-formed scrotal sac.

Gastroduodenostomy.—FLINT (*Lancet*, 1927, i, 12) says that he has practised this operation for chronic duodenal ulcer in a series of close to 200 cases. He emphasizes that it is quite easy to mobilize the duodenum in practically every case. He has performed gastroenterostomy only nine times, largely on account of adhesive difficulties. In all the other cases mobilization was easily accomplished. One detail in technique is important, that is, to free the angle between the second and third parts of the duodenum, where it turns to the left to cross the spine. It is better to free this end of the second part, rather than the upper angle, where the first and second parts meet, as at this point there is often very embarrassing vessels. There have been 2 deaths in this large series. There have been no instances of attacks of discomfort, flatulence and diarrhea following indiscretions in diet. No anastomatic ulcers have occurred in the author's experience when doing gastroduodenostomy for chronic duodenal ulcer. The more physiologic disposition of the parts after gastroduodenostomy probably accounts for the complete freedom from trouble after operation.

The Importance of Toxemia Due to Anaërobie Organisms in Intestinal Obstruction and Peritonitis.—WILLIAMS (*Brit. J. Surg.*, 1926, 14, 295) writes that the hypothesis put forward in the paper is that the toxemia in cases of intestinal obstruction, whether organic or secondary to peritonitis, results in part at least from the absorption of the toxin of *Bacillus welchii*, due to the proliferation of this anaërobie in the stagnant contents of the small intestines. The author discusses the clinical resemblance of the toxemia of intestinal obstruction and peritonitis to that of gas gangrene. Evidence is given of the proliferation of *Bacillus welchii* in the small intestine in cases of intestinal obstruction and peritonitis in human subjects and in these diseases experimentally produced in dogs. Evidence is given of the presence of *Bacillus welchii* toxin in the small intestine in intestinal obstruction and peritonitis in human subjects and in these diseases experimentally produced in dogs. The toxin was not found in normal small intestine contents or in contents of the large intestine, even when obstructed in human subjects. Evidence is given compatible with the absorption of *Bacillus welchii* toxin from the clinical aspect of cases, from the occurrence of hemolysis and from microscopic changes in the heart and liver of fatal cases. The author, moreover, reports a series of cases of appendicular peritonitis and acute intestinal obstruction, in which *Bacillus welchii* antitoxin was administered. Evidence is given in the results of this therapeutic test of clinical benefit in individual series and of improvement of the general mortality note in each series.

PEDIATRICS

UNDER THE CHARGE OF

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Growth in Children with Diabetes Mellitus.—LADD and DAY (*Am. J. Dis. Child.*, 1926, 32, 812) studied 34 cases of diabetes mellitus, all but 4 of whom were either overweight or overgrown, or both, at the time of the onset of the disease. No other significant etiologic factor was noted. In the 2 of these remaining cases diabetes appeared after an acute infection; in 1 the disease was apparently idiopathic. Disease observers noted that growth in height in children with diabetes mellitus diminishes or stops completely, depending upon the severity of the case, and this phenomenon appears to be due to lack of food. The stimuli for growth in height seems to persist longer under the adverse conditions of diabetes, and it also appears to be slower in starting than the stimuli for changes in weight. Insulin enables patients to use sufficient food and growth follows. The best weight for the child is the average weight for height, as expressed in the Bardeen growth curve for normal children, allowing for normal variation of ± 12 per cent. The best food intake is somewhat less, possibly about two-thirds of the total calories of the Holt and Fales standards. The average proportion of carbohydrates, protein and fat of the total calories is: Carbohydrate, 35 per cent; protein, 15 per cent; fat, 50 per cent. The fat in carbohydrate quotients are just about the reverse of the Holt and Fales standard. This is not necessarily the best proportion. Through experience during the last few years, the authors believe that in some cases proportions nearer the normal as given by Holt and Fales yield excellent results. They also feel that regularity in food intake and insulin dosage, both as to amount and to time of ingestion is absolutely essential to the successful progress of the patient.

A Comparison of the Effects of Supplementary Feedings of Fruit and Milk on the Growth in Children.—MORGAN, HATFIELD and TANNER (*Am. J. Dis. Child.*, 1926, 32, 839) examined 47 children living in the California state schools for the deaf and blind during a period of eighteen weeks in the spring of 1925. During this period 13 of these children were given a half pint of milk each day as a supplementary lunch, 13 were given one medium large orange each day, 10 were given four pulled figs each and 11 were used as controls. The degree of underweight, lack of fitness, of these groups when the feeding was begun was in decreasing order—orange, fig, milk and control. Five of the fig group, 2 of the orange group, 1 of the milk and none of the control group suffered an attack of influenza during the experiment. All of the children were served with the same regular meals throughout in the institution's dining room. Judged by the Baldwin-Wood standard

of nutrition, after fourteen weeks of supplementary feeding the milk, orange and fig groups had made almost exactly the same amount of improvement, while the control group had increased only a quarter as much as the other three. Judged by the Pirquet standard, the orange group made the most improvement, the fig and control group about half as much and the milk group had fallen off a little. Judged by the Dreyer standard, the orange group again made the most growth, the control and milk each about half as much and the fig least of all. The average of all these gains shows the orange group first, the fig and milk next and the control group last. The gross gain in pounds was largest for the milk group and the average percentage gain in weight above that expected, according to the whole standard, was largest for the orange and milk groups. Seven children were changed from the milk to the orange lunch, and 7 from the orange to the milk lunch at the end of fourteen weeks, and these feedings were continued for four weeks longer. All gain in weight was considerably decreased in those changed from orange to milk, but very little affected in those changed from milk to orange. The percentage of the original groups showing an increase after fourteen weeks, in standing and sitting, height was greatest in the milk group; in chest circumference, chest expansion and vital capacity, in the fig group; in hand-grip strength, in the orange group. The composition of the house diet was shown to be excellent as to milk and animal protein content, fair as to vegetable content, but somewhat deficient in fruits, especially of the fresh, raw variety. The ash reaction of the diet as eaten was, undoubtedly, acid, and it is possible the supplementing of this as well as of the antiscorbutic content of the diet with the oranges were effective. The value of the figs may lie in their laxative action. The value of extra milk for these children must lie chiefly in the extra caloric value as well as the supplementing of a possibly uneven intake of milk at meals.

Asthma in Children.—PESHKIN (*Am. J. Dis. Child.*, 1926, 32, 862) reports the result of the study of 100 consecutive cases of asthma, in which he found that 22 per cent of the patients had eczema, 7 per cent had urticaria and 2 per cent had angioneurotic edema, making a total incidence of 21 per cent. Urticaria and angioneurotic edema secondary to an eczema were not included in these figures. In 7 to 9 of these patients who were protein sensitive the incidence of eczema was 22 per cent; urticaria, 2.5 per cent; angioneurotic edema, 2.5 per cent. In 21 who were protein nonsensitive the incidence of eczema was 19 per cent; urticaria, 24 per cent; there were no cases of angioneurotic edema. The patients composing the group of allergic asthma type accounted for 55.8 per cent of the total food sensitization. Of these, 7.5 per cent gave no food reaction, another 7.5 per cent reacted only to one or two foods, while the remaining 12 per cent accounted for 52 per cent of the total food reactions. The last group always reacted to foods in biologic groups and the dermatoses were always either eczema or angioneurotic edema. The patients with urticaria did not react to biologic food groups. Eczema always commenced during infancy and always preceded the onset of asthma varying from one to seven years. Angioneurotic edema was concurrent with or followed the onset of asthma. Urticaria always occurred after the onset of asthma. This relation

did not exist in the non-allergic group. Patients with asthma, showing a positive cutaneous food reaction whose eczema had cleared, did not have the recurrence of the asthma with the ingestion of these sensitizing foods. Ingestion of these foods did cause urticaria or angioneurotic edema and occasionally asthma in some cases. Patients with persistent or recurrent eczema were not relieved of the skin condition by elimination of these foods from the diet, but other ingestion resulted in exacerbation of the eczema, and especially in those who were sensitive to biologic food groups. The foods responsible for the greatest number of skin reactions in the dermatosis group were fish, meat, milk and egg. All children with asthma reacting to fish or meat as biologic groups invariably give a history of eczema commencing during infancy. The existing clinical manifestations of hypersensitiveness to fish were mainly referable to the skin and were urticaria, erythema and angioneurotic edema. Hypersensitiveness to meat was manifested in the respiratory tracts; to egg in the gastric intestinal and respiratory tracts and to milk in the gastric intestinal tract and the skin. In infants and young children with eczema reacting to food as a biologic group, it may be possible to prevent asthma by further tests and by elimination of an allergic sensitization which have a direct bearing on the etiology of asthma.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Decline in the Registered Mortality from Syphilis in England—To What is it Due?—This is a notable summary by a public health authority, NEWSHOLME (*J. Social Hyg.*, 1926, 12, 513), of international reputation in the field of venereal disease control, on the progress made in the control of syphilis, as evidenced by the British mortality figures from 1901 to 1925 and the registration in British venereal disease clinics from 1918 to 1925. It appears that the crude annual death rates from syphilitic infections at all ages per 1,000,000 living, as given in Table L of the Registrar General's annual review of England and Wales for the year 1924, indicates that the mortality from syphilis has fallen from 53 in 1901 to 33 in 1924. Mortality from general paralysis of the insane has fallen from 70 in 1901 to 40 in 1924; that from tabes dorsalis has slightly increased from 13 in 1901 to 19 in 1924; aneurysm has decreased from 30 to 26; the combined rate from 166 to 118, and relative figures from 100 to 71, in this lapse of time.

The most striking change is apparent beginning with 1919, when all the rates exhibited the most pronounced drop apparent in years, a decline which has been held consistently or become more pronounced between 1919 and 1924. Sir Arthur Newsholme points out that a revision of these figures, such as Osler suggested, to include the occult death factor from syphilis, would place the disease, with cancer, tuberculosis and pneumonia, as one of the four chief causes of death. The drop in mortality figures has taken place in the face of improved diagnosis and more complete registration. The decline in death rate of 1924 as compared with 1921 amounts to 29 per cent, and when 1917 is compared with 1924 it amounts to 32 per cent. Sir Arthur indicates that the changes in mortality from late complications are indices of the effectiveness of treatment begun a decade ago, while the more recent changes in registered mortality from syphilis as such indicates the effectiveness of the World War campaign. An equally interesting evidence of the effectiveness of the British antivenereal campaign is found in the decline of new cases of gonorrhea and new cases of syphilis in the face of an increased number of clinics and a steadily increased total attendance from 1918 to 1925. In 1917 the total number of government clinics was 113, increased to 193 in 1925. The total attendance increased from 204,692 to 1,719,148. New cases of syphilis in 1918 were 26,912; in 1919, 42,134; in 1925, 22,588. Gonorrhea, on the other hand, has shown a smaller decline, probably because of the lesser effectiveness of medical treatment control in this disease. An interesting incidental observation concerns the comparison of the experience of Portsmouth and Birmingham. In both of these cities there has been a fairly parallel and equal diminution of cases of syphilis and gonorrhea, yet in one of them disinfection as a prophylactic has been publicly advocated and in the other it has not. The author compares his findings with those of Bayet, of Brussels (*La Lutte contre le syphilis en Belgique*, 1926), in which essentially the same experience is recorded for Belgium. The chief feature of the work accomplished in both countries has been *prophylaxis by treatment*. Bayet concludes that arsenical medication has reduced the contagious period in syphilis from three-quarters to four-fifths, although the author questions the accuracy of this estimate. As they stand, the figures constitute the greatest encouragement to workers for venereal disease control which has thus far appeared.

Observations upon the Regulation of Blood-flow Through the Capillaries of the Human Skin.—LEWIS (*Heart*, 1926, 13, 1) investigated the statement of Ebbecke, that when the hand of a susceptible subject is watched in strong sunlight or otherwise warmed whitish and red spots of a few millimeters in diameter are often to be seen. He studied these patterns with a view to determining their permanency. Krogh states that they may continually change in location; Mackenzie, speaking of larger mottlings on the arms and legs, states that they may vary within a few minutes from pallor to congestion. These statements create the impression that the capillaries of the skin are in a constant state of movement individually and in groups, the mottling of the skin changing unceasingly. Comparisons are drawn with the state of capillary activity of the circulation, as described by Krogh on the frog's

web and by Richards on the glomeruli of the kidney. After careful mapping of the pallor patterns and microscopic observation of the behavior of the vascular supply, the author is unable to support the belief that mottling of the skin (livedo) is materially changed by external temperature or heavy venous congestion. Moreover he found little evidence of internal or spontaneous variation from hour to hour or day to day, provided the skin remains under reasonably constant conditions. The tone of the minute vessels, terminal arterioles, capillaries and minute venules treated as a whole is influenced locally by the needs of the tissues which they supply. Friction may cause temporary alteration in the pattern. There is insufficient evidence that any endothelial vessel of this meshwork is influenced as an individual by local needs to an extent which affects very appreciably the flow of blood through it. Owing to the freedom of diffusion in the tissue spaces the influence of local nutrition is exerted over a wider range than this, the vessels being affected as groups rather than individually. There appears to be peripherally a balancing mechanism between the meshwork of minute vessels and the muscular arterioles, whereby a change in the caliber of vessels of the second order, which more than meets the requirements of the tissue supplied, is met by a contrary change in the vessels of the first order. The bloodflow to the tissues is regulated in a twofold manner—by the tone of arteries and muscular arterioles on the one hand; by the tone of endothelial vessels on the other. The first mechanism is under the governance of the nervous system, central and peripheral, and forms a coarse adjustment; the second is controlled more directly by the local tissue needs and forms a fine adjustment of great precision. Mottling of the skin of the palms of the hands and of the skin of the body generally (*cutis marmorata*) is due to local differences in the tone of the minute vessels. These differences are to be coupled with the subdivision of the skin into anatomical areas, the latter being possibly areas of the skin to which the distribution of blood through arterioles is unequal.

OBSTETRICS

UNDER THE CHARGE OF

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When Shall We Treat Retroflexio Version of the Uterus and How?—ANSPACH (*Atlantic Med. J.*, 1927, 30, 214) deals concisely with the

subject and brings up to date the opinions gathered from the mass of literature dealing with these abnormalities. The symptomatology and methods of correction are given in detail. The author gives his attitude regarding retroflexio version in that this condition should be let alone in cases of unmarried women where there are no complications and no symptoms. Further, that it should not be allowed to continue in the married woman who is desirous of children. He states there is nothing which is more often responsible for abortion in young married women than this abnormal condition existing in the uterus. The symptoms of retroflexio version need particular and careful study, so that one may be able to differentiate between retroflexio version and other lesions. The most frequent symptoms given in their order of frequency are backache, lower abdominal distress, menorrhagia, dysmenorrhea, vesicle and rectal disturbances. The first two given are by far the most frequent, and the author lays stress on other conditions which are associated and factors in combination with the abnormality itself. The backache and lower abdominal distress which are particularly due to retroflexio version are definitely aggravated by exertion and relieved by rest. The article goes into the correction of the lesion, the use of the pessary which is often unappreciated, much maligned, misunderstood and badly managed. The operations are not taken up in detail but the principle which underlies many of the operations for this correction are mentioned, and the principles involved for the satisfactory correction are set forth.

Forceps Delivery.—CORNELL (*Surg., Gynec. and Obst.*, 1927, 44, 221) sets forth certain conditions which should be observed before instrumentation and forceps delivery are considered. They are given in their order and explained in the text: (1) The cervix should be fully dilated or dilatable, if not disastrous results will follow; (2) the membranes must be completely ruptured; (3) the child should be alive, although there is an exception to this rule—the extraction of a dead fetus by forceps is sometimes permissible; (4) the head should be engaged and never floating; (5) the mother's condition should be such that a general anesthetic is not contraindicated; (6) the pelvis should be large enough to permit passage of the child. Stress is laid on the prolongation of the second stage of labor which may result in cerebral injury to the child and maternal exhaustion. The technique of preparation is given in detail. For an anesthetic chloroform is ruled out; the author mentions ethylene as a general anesthetic, and is of the belief that ethylene causes the tissues to bleed more readily. Careful instructions are given for catheterization. A comprehensive description of the ironing out or stretching of the perineum is set forth. Rectal examinations are not used. Mid forceps and low forceps are described; high-forceps operations are not performed because of the greatly increased fetal mortality and the severe maternal lacerations and trauma which follow its use; he wisely prefers a version and extraction of these cases, as giving better results. The author describes the episiotomy when performed and the manual rotation of the posterior positions. The completion of the labor after delivery of the head is given in detail and the immediate medication and after treatment, along with the repair of the episiotomy.

Bradytocia.—A term seldom used in obstetrics, and deals particularly with and applies to those long, drawn-out and tedious cases of labor, is bradytocia. It differs from dystocia in that it is not pathologic labor. Five hundred cases of bradytocia were selected by HORNER (*Surg., Gynec. and Obst.*, 1927, 44, 194). The incidence of bradytocia was 10 per cent on over 4000 deliveries, of the time limits which were set as twenty hours for primiparæ and fourteen hours for multiparæ. One case in every 10 was prolonged labor. The highest percentage was found among American born, being 60 per cent. It occurs more frequently in primiparæ, between the age of nineteen to thirty years. No definite etiologic factor is given, but a combination of conditions that influence the prolongation of labor are given for its existence. Chief among them are the early rupture of membranes, over term pregnancies and primary inertia. A deficiency of innervation of the uterine musculature in the young gravidæ seems to delay the function of the uterus when labor begins. The diagnosis of bradytocia begins in the prenatal period by the general examination of the patient's physical construction, pelvic anatomy and in the latter months by fetometry. The maternal morbidity in prolonged labor is necessarily high, as a prolonged labor lowers the patient's resistive power and consequently reduces her chance of withstanding infection. Watchful expectancy of these cases is at present the method of choice, but the future may hold some change as time and methods advance. The conclusions drawn are those of prophylaxis. The selecting of cases unfit for normal labor. The test of labor and its essentials as to what is a sufficient test of labor. The operative interference and justification in its procedure. The shortening of the first stage of labor if possible and the termination of the second stage after a lapse of two hours. There is still much to be discussed and adjusted in handling bradytocia cases.

GYNECOLOGY

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Roentgenography of the Fallopian Tubes.—In presenting their technique and experiences with the injection of lipiodol for the purpose of making roentgenograms of the Fallopian tubes, MCCREADY and RYAN (*Am. J. Roentgenol.*, 1926, 16, 321) state that the unsatisfactory results of operation for the relief of sterility depend largely upon the inability of the gynecologist to make an exact diagnosis of the actual pathologic condition of the tubes before operation. It necessarily follows that many cases are operated upon uselessly. Until the advent of the

Rubin test, even the diagnosis of patency of the tubes was not possible. Insufflation of the tubes was a marked advance, but even this test does not indicate the point of occlusion, a very important factor in determining the indication for operation. The farther out from the uterus the occlusion exists, the better the chances for the success of the operation. They believe that the results of roentgenography of the tubes can be thoroughly relied upon if conducted with proper care and attention. This method will not only make the diagnosis of patency, but if the tubes are obstructed the point of occlusion can be accurately demonstrated. They describe their technique, which is quite simple, and presents many beautiful examples of visualization of the tubes, both normal and pathologic.

Hemorrhage of Puberty.—The menstrual irregularities and hemorrhages which occur at the time of puberty have always been of much interest to the gynecologist, and until quite recently have often been rather troublesome to treat successfully. It is of interest, therefore, to review a study on this subject which was made by WOLFE (*Am. J. Obst. and Gynec.*, 1926, 12, 45), as the result of which he states that puberty hemorrhage is a definite clinical entity presenting as a menorrhagia or metrorrhagia in the absence of inflammation, neoplasia or the pregnant state. The soft patulous cervix is pathognomonic; the body may or may not be enlarged. Symptoms recur after curettage, but are always controlled by radium. Curettings are abundant, thickened and frequently polypoid. This is the result of a diffuse glandular, stromal and vascular hyperplasia. Persistence of solitary ripening follicles or simultaneous maturation of multiple follicles accentuates a physiologic endometrial hyperplasia into a pathologic type. These changes have been experimentally reproduced in laboratory animals. Corpus luteum formation is absent. The uterus is the direct seat of bleeding. It results from thrombosis of the endometrial vessels and ensuing necrobiosis, and from actual mechanical rupture of engorged capillaries. The factors inaugurating persisting, follicular cysts in the ovary with its concomitant endometrial hyperplasia remain a subject for future study.

Results of Operations for Uterine Prolapse.—One of the most important contributions that the large clinics can make to the progress of surgery is the periodical analysis and report on the end results which are obtained following various operative procedures. In the days before follow-up clinics were held, many patients were discharged from hospitals as cured, but in a short time the original trouble returned and the surgeons were never aware of their failures and consequently had distorted ideas of the value of certain operations. A comparative study of the end results of the various operations for prolapse of the uterus done between 1915 and 1925 at the Woman's Hospital in New York has been presented by BULLARD (*Am. J. Obst. and Gynec.*, 1926, 11, 623) in which there are 361 cases which were operated upon by 30 different operators. Every patient had been examined by the surgeon who operated upon her and by some other member of the visiting staff at least once since her operation and a large majority of them have been observed several years in the follow-up clinic. The survey shows that

95 per cent of the cases are cured by vaginal plastic surgery. The vaginal plastic work combined with ligament shortenings from above is satisfactory perhaps in cases of slight prolapse, but the careful fascial reconstruction by vagina undoubtedly is responsible for the success. He states that the majority of the gynecologists of today have long since ceased to attempt to cure descent of the uterus by any form of suspension or fixation by the abdominal route. Careful reconstruction of the various planes of the pelvic fascia that have become attenuated, overstretched or torn is the *sine qua non* of the operative treatment of prolapse. In this series the Watkins operation has not been followed by enterocele but there is a considerable percentage of cases with bladder symptoms. The Mayo operation has been extremely satisfactory except for an occasional enterocele. Vaginal hysterectomy has been most satisfactory.

Cervical Cauterization Preceding Hysterectomy.—The theoretical danger of the retained cervical stump following hysterectomy has been handled by CASHMAN (*Am. J. Obst. and Gynec.*, 1926, 12, 591) for some years by the use of the cautery. He uses it not only as a preliminary to hysterectomy but also in practically all operations for infected tubes and in cervicitis without intraabdominal complications. He has not seen a case of carcinoma develop in a cervix treated in this manner although he has seen 3 cases in the past two years in patients who had had pelvic operations but in whom a diseased cervix was neglected. The technique which he uses differs from that originally advocated by Hunner since the cauterization is completed at one sitting. The cervix is dilated and the entire cervical canal is cauterized, and deep radial incisions are made at the external os, extending well onto the vaginal portions of the cervix, thus destroying the cone-shaped, gland-bearing portion of the cervix by a simple rapid method. If this be done as the first step is subtotal hysterectomy, there is accomplished practically all that is accomplished in total hysterectomy and the disadvantages of total hysterectomy are eliminated. As a result of this procedure, the cervical mucosa and glands are destroyed, the cervix heals smoothly without a lumen and no after-treatment is necessary and moreover the normal vault of the vagina is preserved.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Optic Nystagmus and its Value in the Localization of Cerebral Lesions.—FOX and HOLMES (*Brain*, 1926, 49, 333) employ the term "optic nystagmus" to designate that regular movement of the eye

induced by observing figures on a rotating drum consisting of a slow component in the direction of rotation of the drum and a quick component in the opposite direction. Bárány believes the phenomenon is of cerebral origin, and suggested that the slow phase is activated from the gyrus angularis and the quick phase is activated from the frontal lobe. Stenvers believes that it is a cerebral reflex subserved by a path between the occipital pole or the calcarine region and the frontal lobe, and that it is lost toward the opposite side when a lesion damages either of these centers or the pathway between them. The aim of the authors' investigation was to determine if an absence or a modification of optic nystagmus to the one side has any value in the localization of cerebral lesions. Their observations were made on 41 cases of cerebral tumor, in 24 of which the site of the lesion was verified by either operation or postmortem examination. They concluded: "That a unilateral lesion of the forebrain can disturb lateral optic nystagmus to the opposite side only. If the lesion lies in the right hemisphere clockwise rotation of the drum evokes a nystagmus, consisting of slow deviation of the eyes to the left and quick jerks to the right; in other words, a nystagmus to the right; but anticlockwise rotation has no effect, or produces a less regular or less pronounced nystagmus to the left." While to any definite conclusion some of their cases presented obvious exceptions, it seemed that nystagmus to the opposite side is effected when a lesion lies in the supramarginal or angular gyrus, in the adjacent portion of the parietal and temporal lobes, in the posterior end of the second convolution or along the line joining this with the angular gyrus. Their observations tend to support Stenvers' hypothesis, that reflex centers for optic nystagmus lie in the occipital lobe and in the second frontal convolution and that these are connected by a reflex path which runs through the white matter of the hemisphere.

Sclerosis of the Central Artery of the Retina.—BRIDGETT (*Am. J. Ophthalm.*, 1926, 9, 725) made histologic examination of the central arteries of the retina, obtained postmortem, from 200 patients. This examination disclosed normal vessels in 45.5 per cent excessive physiologic thickening in 21.5 per cent, arteriosclerosis proper in 26 per cent, syphilitic arteritis in 1.5 per cent and periarteritis in 5 per cent. The development of the subendothelial layer of the central artery normally reached a maximum about the fourth or fifth decade; excessive thickening, not accompanied by degenerative changes was found in about one-fifth of the arteries. The true arteriosclerotic lesions were similar to those occurring in other vessels of like caliber, but usually a slight degree. The periarterial lesions were most frequently found in relation to local or general infection. Sclerosis of the central arteries occurred only one-third as frequently as did the sclerosis of the aorta, the coronaries and the brain arteries. Conversely, when the aorta, coronaries and brain arteries were grossly normal sclerosis of the central arteries was found in 18 per cent of the cases. In 22 cases histopathologic differences were found between the right and left central arteries. Sclerotic changes occurred a little over twice as frequently in the extraneural as in the intraneural part of the vessels. Considerable disagreement was found to exist between clinical and histologic observations. The fact that vascular sclerosis usually does not involve

the arterial system uniformly deserves emphasis. In retinal arteriosclerosis of persons between the ages of nineteen and forty-two years of age syphilis was the most frequent constitutional disease. In all age groups the number of cases with normal predominated over those with sclerosed central arteries. The incidence of sclerosis was somewhat higher in females than in males.

RADIOLOGY

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Ulcer of the Duodenum.—In considering the problems connected with ulcer, JUDD (*Minnesota Med.*, 1926, 14, 320) states it is first necessary to separate the gastric from the duodenal. The gastric ulcer may be malignant; in the case of duodenal ulcer the question of malignancy may be disregarded. Primary carcinoma of the duodenum that resembles an ulcer is almost unknown. Ulcers of the duodenum are usually situated on the anterior surface in the cap; occasionally they are found on the lower border and rarely on the posterior wall, some distance from the pylorus. Because of their proximity to the pancreaticoduodenal vessels, ulcers in this region are frequently the cause of severe gastrointestinal hemorrhages. It is not unusual in opening the duodenum to find a small spot of puckering, congested, mucous membrane just opposite the anterior ulcer. Lesions in the duodenum, as seen in the operating room, are of two distinct types—one a true chronic ulcer with a crater, which has lost a certain amount of mucous membrane and the other not a true ulcer but a localized area of inflammation. Duodenal ulcers occur much more frequently in males than in females and patients most often present themselves for treatment at middle age. Jewish people apparently have a greater tendency to duodenal ulcer than do other races. Physiologic activity has to do with the cause of an ulcer and infection with certain strains of bacteria plays an important role. Experimental evidence is that acid secretion comes from the glands at the cardia and that secondary ulcers may follow resection, just as they follow gastroenterostomy. If excision of the ulcer with reduction of the sphincter activity can be performed just as safely as gastroenterostomy, this is the operation of choice. This is dependent on the mobility of the duodenum; if the upper edge of the duodenum is bound down as a result of inflammatory adhesions it is usually not advisable to attempt to excise the ulcer. At present he is excising 50 per cent of duodenal ulcers and has had more than 90 per cent of cases showing complete and permanent relief

from all symptoms. A number of bleeding ulcers continue to bleed at intervals after gastroenterostomy; therefore, the radical operation is preferable in cases of duodenal ulcer in which severe bleeding has occurred.

Massive Collapse of the Lung.—Massive collapse of the lung is a shrunk, airless condition of a part or all of one or both lungs, occurring suddenly after operation or injury below the neck, without the direct application of external force, or demonstrable obstruction of the air passages. Essentially it is the same as pulmonary atelectasis; it differs only in that its onset is abrupt, that it usually is lobar in distribution and that it is intimately associated with some form of trauma. RIGLER (*Minnesota Med.*, 1926, 6, 326) reviews the literature, crediting Pasteur with first calling attention to the condition of 1890 in cases of postdiphtheritic paralysis of the diaphragm, and in 1908 noting it following abdominal operations. The most reasonable theory would support a combination of respiratory immobility and bronchial obstruction as the cause. The close resemblance of massive collapse and atelectasis following foreign body strengthens this view. Bronchoscopy, with removal of a plug and subsequent cleaning of the collapsed lung, has been done. The onset may be sudden, usually within twenty-four to seventy-two hours after operation or trauma; or, more often, slow with dyspnea and cyanosis the most prominent findings. In the fulminating cases it closely resembles pulmonary embolism. The clinical course is most frequently mild, lasting three to six days. It is notable that no case of unilateral collapse without complications has ever proved fatal. The lung is heavy, shrunk and does not crepitate, the alveoli are collapsed and there may be fluid in the bronchi. The ingress of air is interfered with; the circulation remains intact, the air is absorbed and the lung gradually shrinks down. The diaphragm in the affected side moves upward, the mediastinum moves toward the affected side. The roentgenographic is the best diagnostic method of demonstrating the lesion.

The Newer Clinical Aspects of Gastric Carcinoma.—The traditional conception of gastric carcinoma from the standpoint of diagnosis and prognosis is in need of revision in the light of modern medical progress, asserts EUSTERMAN (*Radiology*, 1926, 6, 409). The pathologist's conception of the evidence of the malignant transformation of a benign ulcer, and the roentgenologist's recognition and localization of circumscribed lesions, with an estimate of their probable size and extent have made possible earlier recognition of the actual and potential malignant processes in the stomach. Comparing two sets of statistics, one compiled in 1914 by Friedenwald and another from the material of the Mayo Clinic seven years later, he points out that malignant lesions were detected at an earlier and more operable stage in the second series. Exclusive of the more obstructing small lesions, and of some of larger extent in a high-lying stomach, the majority of cases of gastric carcinoma are readily diagnosable as such on the basis of history, physical examination and gastric analysis. Malignant transformation of a benign ulcer may be suggested by: (1) Loss of periodicity of attacks (attacks are longer and intervals of relief shorter); (2) loss of periodicity

of pain, the pain tending to persist after eating; (3) less severe pain, but a more constant dull ache, increased by eating; (4) loss of appetite, which may ensue even when the test meal shows the high acidity characteristic of ulcer; (5) variation in the vomiting, which may diminish in amount and frequency, although it is rarely increased, unless there is obstruction; (6) diminution in gastric acidity; (7) persistent occult blood in the feces. Roentgenologic indications of malignancy, such as the niche type of ulcer with an unusually large crater and the demonstration of ulcerating carcinoma with a meniscus-like crater, constitute a significant advance.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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A Case of Herpes Zoster, Apparently Due to Invasion of the Ganglia by Round-cell Sarcoma.—MORTON (*J. Neurol. and Psychopath.*, 1926, 6, 296) reports a case in which sarcoma cells form nodules on the left side, and had spread and invaded the fifth and sixth dorsal ganglia on the right side (probably through the lymphatics). A disturbance of a herpes zoster due to specific virus formed; it would seem, therefore, that herpes zoster results from injury to the dorsal ganglion whether caused by an acute specific virus or some other form of trauma.

The Operative Treatment of Gastric Crises.—CRITCHLEY and WOLFSOHN (*J. Neurol. and Psychopath.*, 1926, 5, 318) believe that following a careful review of the cases treated by operative procedures and the study of several cases it is probably necessary to carefully differentiate between crises of vagal and those of sympathetic origin or both. Section of the gastric branches of the vagus combined with gastrojejunostomy possibly affords greatest relief in vagal cases. In sympathetic cases chordotomy, or section of the anterolateral tracts, for relief of pain is least dangerous. In some crises section of the vagus will effect a cure.

Yellow Spinal Fluid Associated with Tumor of the Brain.—COMFORT (*Arch. Neurol. and Psychiat.*, 1926, 15, 751) states that xanthochromic fluid probably has definite significance in the localization and prognosis of brain tumors, occurring as it did in about 20 per cent of the cases studied. Xanthochromia, probably hemolytic in origin, when associated with tumor of the brain indicates the involvement of the ventricular or external surface of the brain, and that the tumor is soft and vascular or surrounded by engorged vessels. The hemorrhages causing the

coloration are believed to be small and repeated. Xanthochromia occurring with many erythrocytes, indicating a soft vascular tumor, is possibly a contraindication for procedures lowering intraventricular pressure.

Tryparsamid in the Treatment of Late Neurosyphilis.—MOORE and SUTTON (*J. Nerv. and Ment. Dis.*, 1926, 63, 569) believe that in late neurosyphilis the treatment should be primarily to build up resistance, hence the value of tryparsamid which is too weak a tryponemacide for use in early syphilis. Patients who have received intensive treatment with mercury and arsphenamins show more striking improvement than individuals who have received no preparatory treatment. It should never be forgotten, however, that tryparsamid carries a menace to the optic nerve and suitable tests and examinations should be regularly carried out.

Somnolence: Its Occurrence and Significance in Cerebral Neoplasms.—The value of somnolence as a diagnostic sign in intracranial neoplasms is discussed by MCKENDREE and FEMIER (*Arch. Neurol. and Psychiat.*, 1927, 17, 44) in a review of 100 cases. The authors found this symptom present in 32 of the cases reviewed. The difficulty of differentiating between epidemic encephalitis and brain tumor in some cases was noted. They found that somnolence is not valuable as a differential point in regard to anatomic region involved, the age or the type of the tumor. It was most constantly found in cases exhibiting marked internal hydrocephalus. They believe that increased intracranial pressure, with or without ventricular distention, operates in producing this symptom.

Crime and its Causes.—TAIT (*J. Abnor. and Social Psychol.*, 1926, 21, 234) believes that mentally defective and psychopathic individuals appear more frequently in one court, not because they commit more crimes, but because they are apprehended oftener. He describes the activity of certain social organizations interested in the investigation of crime, and believes there is a causal connection between the increase in crime and the reform measures for the management of criminals advocated by such organizations. The home, where the habits which should inhibit the primitive instincts that are frequently antisocial are established, has disintegrated with the externalizations of society. He believes crime can be controlled only by appropriate treatment in the form of punishment.

Tuberculoma of the Brain: its Incidence among Intracranial Tumors and its Surgical Aspects.—VAN WAGENEN (*Arch. Neurol. and Psychiat.*, 1927, 17, 1), in a report from Dr. Cushing's Clinic, summarizes surgical experiences with intracranial tuberculomas. His report covers 17 cases: 6 cases were exposed and extirpation accomplished or attempted; 8 cases in which a lesion was not exposed or removed, but the diagnosis was verified at autopsy; 3 cases in which the presumed tuberculoma was not verified. Although the extirpation of tuberculomas in the first group was accomplished, the patients uniformly succumbed several weeks following operation, usually due to terminal tuberculous men-

ingitis. Only 1 patient survived for a period of a year and finally died from the effects of an operation for peritoneal tuberculosis. The author justly concludes his report by questioning the advisability of an operation with this type of brain tumor. The article is also of interest in that it indicates that previous statistics regarding the occurrence of tuberculoma in the brain were inaccurate. In a series of 1000 verified tumors only 1.4 per cent were of this type. Permanent recoveries are exceedingly rare. These tumors usually are located in the cerebellum or brain stem.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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A Study of the Pathologic Changes in Scarlet Fever.—An anatomic-pathologic investigation of 32 cases of scarlet fever carried out by SYSAK (*Virchow's Arch. f. path. Anat.*, 1926, 259, 647) stresses the relationship of the disease to glomerular and interstitial nephritis, to fat and iron depositions, and he discusses whether the streptococcus is the etiologic factor or a biologic accompaniment of the causative agent. He made blood cultures from 64 autopsy cases and found only 4 without bacteria, and in every positive case streptococcus was found alone, except where staphylococcus was present as a contaminant. Like many of the recent workers, represented by Lubarsch, he believed he found great variations in the streptococcus, dependent upon their environment, such as a loss of hemolysis, paralleling a return of the power to ferment mannite and a change of the hemolytic strain into a nonhemolytic after intraperitoneal inoculation into a mouse. The author found that on culture all the variations were of a minus order, as illustrated by a loss of virulence. On histologic section the deposition of iron was found in the spleen and tongue, but not in the pancreas. The fat was mostly in the form of cholesterol esters and was present in the heart in 50 per cent, more often in the spleen in phagocytizing cells, also in the pancreas, liver, tongue and testes. On the other hand, the adrenal cortex showed a marked depletion of the fat, the residuum being found in the zona glomerulosa. This impoverishment the author regards as indicating the low level of fat in the blood, and this may be the cause of death in scarlet fever as in other acute infections, that is, the fat loss produces a hypofunction of the adrenals. The degree of fat deposit was dependent upon the presence of complications and

their severity. Likewise the amount of round-cell infiltration was related to the superimposed infections, and it was found that the mast cell was particularly characteristic of the uncomplicated cases of scarlet fever. The kidney changes were localized largely in the loops of Henle and the convoluted tubules, seldom involving the pyramids. Hemorrhage was frequent, and the primary changes specific to the disease were interstitial and the exudative glomerular changes were consequent upon complications or a congenitally vulnerable organ. The pathologic process of scarlet fever is largely in the lymph system and the mast cell is the significant cell in the "perivascular granulomas" which are characteristic of this acute exanthem.

The Venereal or Inguinal Granuloma.—This infective disease has long been recognized in the East Indies and in America, but is practically unknown in Europe. GOLDZIEHER and PECK (*Virchow's Arch. f. path. Anat.*, 1926, 259, 795) report from their New York clinic a number of cases showing an infective process involving the genitals and environs. The incubation period of these cases was about three weeks. The first appearance is a subcutaneous hard, brawny swelling, which frequently progresses to ulceration. This may persist as a chronic inflammation, lasting in one case as long as twenty-six years. The lesion appears as a flat, definitely margined swelling, somewhat cupped in contour and extending centrifugally from the primary site on the genitals. The surface of the granuloma bleeds readily and an abundant watery exudate is formed which often becomes purulent. It also often becomes painful. The infiltrative cells are mainly neutrophils and eosinophils, but the more characteristic forms are plasma cells and large mononuclears with a waxy protoplasm, the latter being frequently the predominant type. These plasma and large mononuclear cells are similar to those described by Mikulicz, as found in rhinoscleroma, both being phagocytic; but the latter localizes on mucous membranes rather than on the skin surface. In the granulomas a pleomorphic organism was seen which was difficult to identify, but 5 of the 7 cases gave bacterium on culture. This bacterium appeared to belong to the Friedländer group, but was distinctive from it in its lack of capsule and in the abundant fat produced, which gave the cultures the odor of rancid butter. It ranged in appearance from a coccoid to a bacillary form with metachromatic granules. Complement-fixation and agglutination tests further differentiated the granuloma organism from the Friedländer bacillus and skin tests and vaccine produced immunities supporting the claim that it is the etiologic factor in inguinal granuloma. They found that the intravenous injections of tartar emetic, used for a sufficient period, was a specific remedy for the condition.

Auricular Endocarditis of Rheumatic Origin.—MacCallum, in 1924, drew attention to certain changes in the wall of the left auricle in rheumatic disease of the heart. They consisted in scarlike thickened patches, histologically showing cellular infiltration and large Aschoff bodies. Now VON GLAHN (*Am. J. Path.*, 1926, 2, 1) reviews 31 cases of rheumatic valvular endocarditis and finds in 9 of them similar involvement of the left auricle. In 1 of these the right auricle was likewise affected; the whole 9 showed left auricular endocarditis. In

the gross, the changes usually occupied a small area just above the posterior leaflet of the mitral valve. This was marked by low, irregular ridges closely crowded together in a furrowed appearance. The surface may be smooth and glistening or roughened by tiny, dull, yellowish flecks. The older lesions are grayer and translucent. More marked cases show flat or delicately ridged plaques of yellow color in many parts of the auricle. In the later stages deposits of calcium occur in the superficial parts. Histologically, large accumulations of small mononuclear cells, many polymorphonuclears and a few eosinophils are found in the outer half of the endocardium. More striking still are collections of large cells with a faintly blue cytoplasm with oval, occasionally slightly lobed or stellate nuclei rather vesicular in character. They resemble the large cells that form Aschoff bodies in the myocardium. These cells often take up positions perpendicular to bands of hyalin-like material which lie in the elastic connective-tissue layer. The endothelium over the sites of these changes is usually intact, at other times a thin layer of fibrin appears on the surface. In the acute stages edema and fibrin in varying amounts separate the elastic fibers. Bacteria have not been demonstrated. Healing and repair occurs by fibrosis; the characteristic cells disappear and calcium not infrequently is present.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Community Responsibility of Hospitals.—LEWINSKI-CORWIN (*Pub. Health Repts.*, 1926, 41, 605) discusses certain points in the responsibility of "community hospitals," which are defined as hospitals from which "no profit can come to the hospital corporation." Policy: This will be based upon: (1) Morbidity prevalence of the community; (2) extent and character of services already available; (3) proportion of private, semiprivate and ward services; also there should be considered the care of outpatients, convalescents and chronic cases. Discharge of implied moral obligation: Professional service—attending, resident and nursing are to be determined on the basis of merit and no negligence, discourtesy or discrimination are to be tolerated. High type of performance: The important feature which differentiates the treatment in the hospital from that in the patient's home is the opportunity it offers for organized and supervised teamwork, for critical analysis of

the performance and for the advancement of the standards of medical education and practice in the community. This assurance to the community that the practice of medicine in the hospital is of the highest type attainable and that it sets the pace and promotes the best type of general practice in the community constitutes the civic responsibility of the hospital, which is of equal importance with that of the actual care of the sick within the hospital. Broader hospital opportunities for physicians: The physicians of the country must be supplied with opportunities for periodic contact with the best hospital practice. This is not an argument for "open" hospitals but for better utilization of the facilities of "closed" ones. The responsibility for training interns is mentioned. Delimitation of responsibility for nurse training: The obligation here is met by providing the best possible facilities for training, by inculcating a spirit of genuine service, and by making living and working conditions as satisfactory as possible. More interest should be taken in the training of "nurse attendants," duties of which require less education and less training than for registered nurses. Availability of hospital facts: The annual report should deal with the services rendered—it should show what the hospital has accomplished, not be merely a collection of medical statistics. It should be directed to the laity. Need of morbidity statistics. The vast reservoir of hospital statistics is not used to the best advantage of the community. A central bureau in large cities is advocated, with statistical service available to member hospitals. The units should be strictly comparable. Provisions for institutional convalescence and for the reclamation of the "chronics:" The importance of convalescent care is stressed and provision should be made to have it institutional in many cases. The chronic cases are inadequately cared for at present. There is a need for institutions for the chronically but not hopelessly ill who so often could be salvaged but who are likely to become victims of charlatans and cults. Provision for contagious disease isolation: Isolation units are required to meet emergencies in contagious diseases. Participation in health promotion: Periodic medical examinations and other health measures should be promoted.

Inherited Immunity in Tuberculosis.—CARTER (*Am. Rev. Tuberc.*, 1926, 13, 373) states that in a comparison and study of some 5000 white patients at Catawba and Blue Ridge Sanatoria and 1700 colored patients treated under the same conditions at Piedmont Sanatorium results obtained in the whites are persistently better than the results shown for the colored. The mulatto negro also shows better results than those in the negro, but not as good as those in the white. The average age of persons treated is greatest in the white and least in the black. The mulatto occupies the middle ground. In the average age at death the results are like the former, highest in the white and lowest in the black race. The greatest incidence of tuberculosis occurs under thirty years of age in the black, next in the mulatto and least in the white. Over thirty the order is reversed. Environment may account for the difference between the black and white races, but this cannot be said of the mulatto and black. The conclusions drawn are that this better resistance, in the instances of the whites and mulattoes, is due to an inherited immunity from an ancestry that has accumulated that

immunity through contact with tuberculosis. The white races transmitting to the mulatto a part of stronger immunity accumulated through longer contact, this transmitted immunity plus that acquired by the mulatto gives him a better resistance to tuberculosis than the black whose immunity has been accumulated entirely by him since being in contact with civilization and almost entirely in the last seventy-five years since freedom has thrown him in contact with crowded centers of population.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 21, 1927

The Effect of Industrial Waste Gases on Plants.—RODNEY H. TRUE (from the Department of Botany, University of Pennsylvania). The development of industries in agricultural or forested areas sometimes gives rise to important problems in plant physiology and pathology. Several classes of industrial wastes have been found to be harmful to plant and animal life. Smelters sometimes give off mineral dusts that go into solution after they have settled on vegetation and cause injury to the plants and to animals grazing on them. Lead has been connected with one such case. The non-toxic dust from cement factories has been known to accumulate on the leaves of fruit trees and probably of other plants also to such an extent as to reduce the light supply to the chlorophyll-containing tissue and in some cases to block the stomata more or less completely.

Acid mists, in which sulphurous and sulphuric acids are borne in solution in water particles may be driven by air currents to considerable distances and when repeated often enough cause harm to plants. Such mists are sometimes irritating to the throat and cause an impulse to cough. Gases are sometimes given off in sufficient quantity to cause injury to plants. SO_2 is most frequently met with. This gas can be smelled in a concentration of from 3 to 5 or more parts per million according to the training and sensitiveness of the individual. This concentration is always potentially injurious to vegetation. If the "stream" of gas continues to lie across a given area for more than a brief period, or if repeated often enough injury is likely to occur. Ten parts per million give a marked odor of burning sulphur and is highly dangerous to plants. Plants vary widely in susceptibility to this gas in respect to the species in general, in respect to the stage of development and in respect to different parts of the plant. In most cases the older leaves are more sensitive to SO_2 than buds and younger leaves. Illuminating gas is also injurious to most plants; CO may easily reach harmful concentrations. Ethylene, sometimes used to enrich illuminating gas, produces striking results in some plants at great dilution. Buds

of carnation flowers will not open in an atmosphere containing 1 part per million and flowers already open will "go to sleep" after 12 hours of exposure. Sweet pea seedlings, grown in complete darkness, undergo strange distortions in 1 part per 10 million parts of air. Castor oil plants change the position in which the leaves are held in a like dilution. Ethylene tends to cause the disappearance of chlorophyll from green structures and has been used to hasten the development of yellow color in green lemons. It has also been found to cause celery to bleach rapidly when 1 to 10 parts are used in 10,000 parts of air.

The Relationship of Basal Metabolism to the Output of the Normal Urinary Pigment.—D. L. DRABKIN (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania). The experimental results of a comprehensive study of the normal urinary pigment, "urochrome" (*J. Biol. Chem.*, 1926, 40, 68), have led the writer to conclude that the quantity of pigment output is essentially independent of the diet and directly proportional to the basal metabolism (as calculated from the surface area in the normal rat, dog and man). The ability to markedly increase the output of pigment, by increasing the rate of basal metabolism with such agents as thyroxin suggested the desirability of supplementing the experimental evidence by a study of pathologic individuals, especially those with diseases characterized by abnormal heat production (Graves' disease, fevers, and so forth). In order to interpret clinical data correctly it was essential to have some idea of the quantity of pigment eliminated by normal subjects. The fact that the pigment output was directly proportional to the surface area in many normal subjects of widely varying sizes (including three different species) was brought out by plotting the output of pigment against the surface area. This chart was utilized for deriving the normal pigment value of the particular individual under observation. A new series of cases, including 10 patients with Graves' disease, 1 with leukemia and 3 with lobar pneumonia, has been intensively studied, under controlled conditions. The pigment output was determined colorimetrically upon twenty-four-hour urine specimens (the reliability of collections being checked up by creatinine determinations). The determinations in all instances were upon consecutive days, in some cases over hospitalization periods two to three months long. In the Graves' disease and leukemia cases, metabolism determinations were made from time to time so as to permit a comparison of changes in output of pigment and metabolic rate.

In the exophthalmic goiter patients a distinct parallelism of the per cent increase in urinary pigment output and in basal metabolic rate was found. In a case which proved resistant to therapy both pigment output and basal metabolism persisted at levels far above normal. In another patient, where response to treatment was clinically apparent, and in whom the basal metabolism gradually fell towards normal, the pigment output also fell. In several individuals, after thyroidectomy, the urinary pigment fell to the normal or, indeed, somewhat below the calculated normal level. In the leukemia case, the relationship of pigment output and basal metabolism was similar to that observed in the thyroid patients. During the pyrexia stage of pneumonia the output of the urinary pigment was above normal, although the magnitude of the increase was of a lower order than in severe exophthalmic

goiter. In pneumonia urines extraneous pigments, such as urobilin and hematoporphyrin, were found to be excreted in appreciable and varying quantities so that they had to be removed in order to obtain a correct value for the normal urinary pigment output.

The data obtained from these carefully controlled clinical cases have fortified the conclusions, which the writer has reached upon the basis of his experimental studies. The output of the normal pigment of the urine is probably proportional to the intensity of the endogenous metabolism.

The clinical cases were supplied through the coöperation of Dr. Nellis B. Foster and his staff at the New York Hospital, Cornell University Medical School.

Anatomic Changes in the Kidneys of Rabbits following Administration of Novasurol and Salyrgan.—S. P. REIMANN and F. WINKELMANN (from the Research Institute of the Lankenau Hospital, Philadelphia). Novasurol, first used as an antiluetic measure, was found to possess marked diuretic properties. Certain disadvantages led to the production of salyrgan which contains approximately the same amount of mercury, 35 per cent, but is apparently less toxic. The chief mode of action of both is the production of a water and salt diuresis, probably by action on both the tissues and the kidneys. Since they contain mercury, they must be administered with caution; the field of usefulness is in cardiac edema with minor changes in the kidneys. Chemical studies can be found in the literature. Given to rabbits, the drugs produce a typical mercurial tubular nephritis with necrosis, disintegration and calcification in the tubules, especially the convoluted tubules and the ascending limbs of Henle's loop. The changes begin on the second to third day. Rabbits were killed at daily intervals after administration of the drug. Some animals died from the effects of overdosage in eight to ten days. Only animals in which preliminary functional tests had shown normal kidneys were used. The dose administered was relatively three to four times that used clinically.

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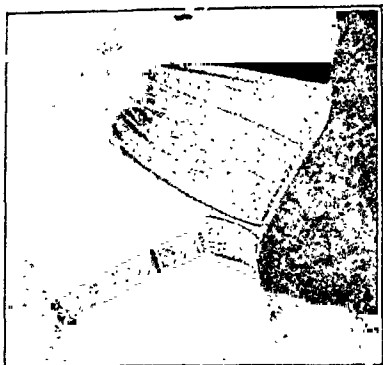
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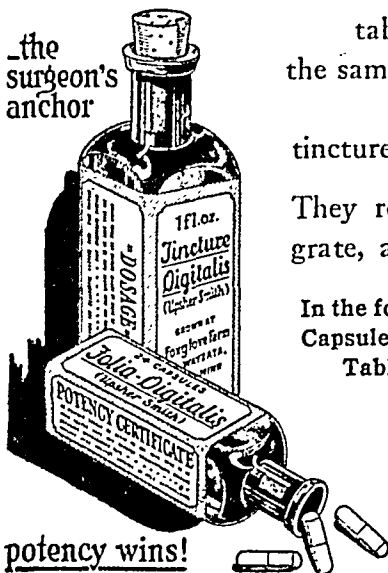
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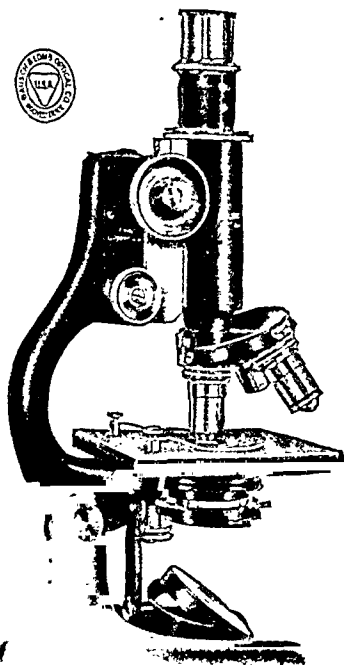
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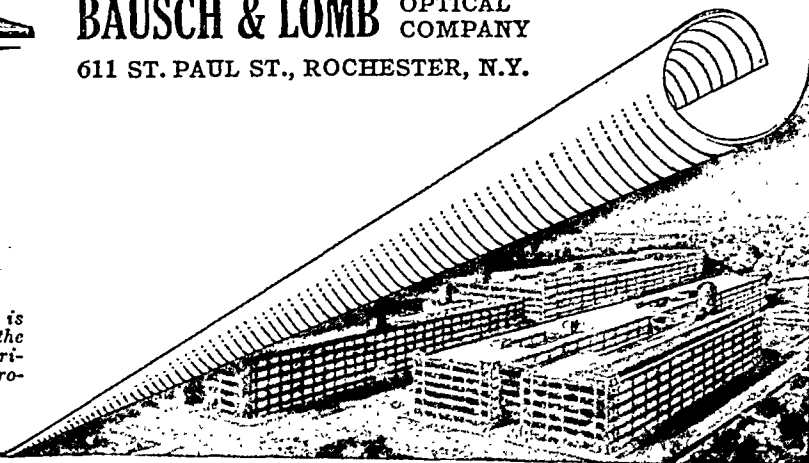
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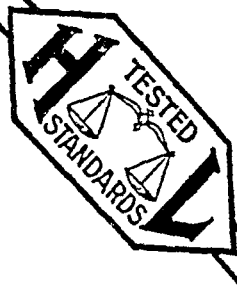
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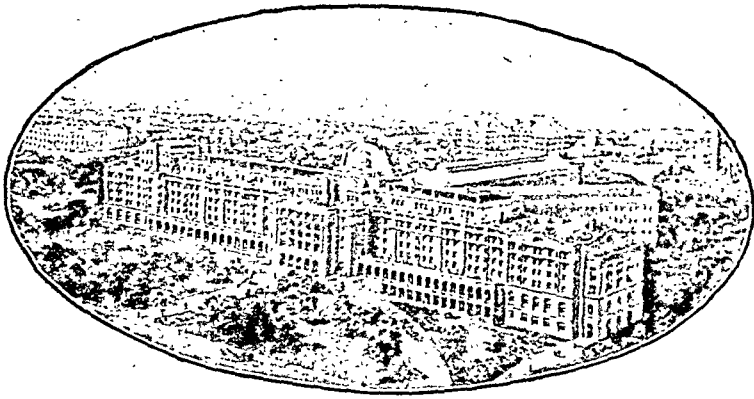
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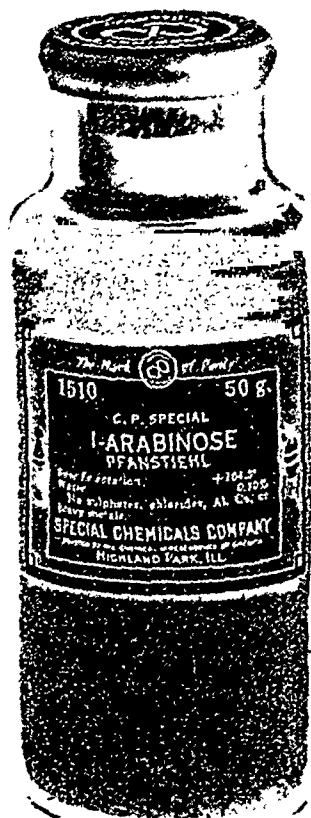
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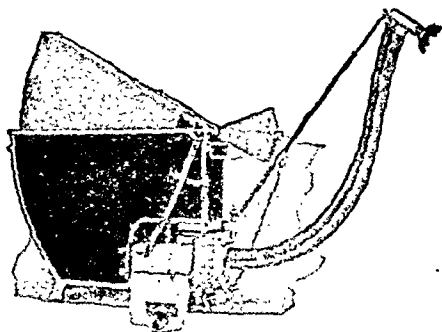
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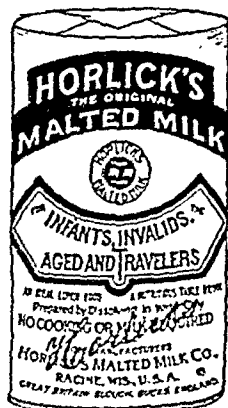
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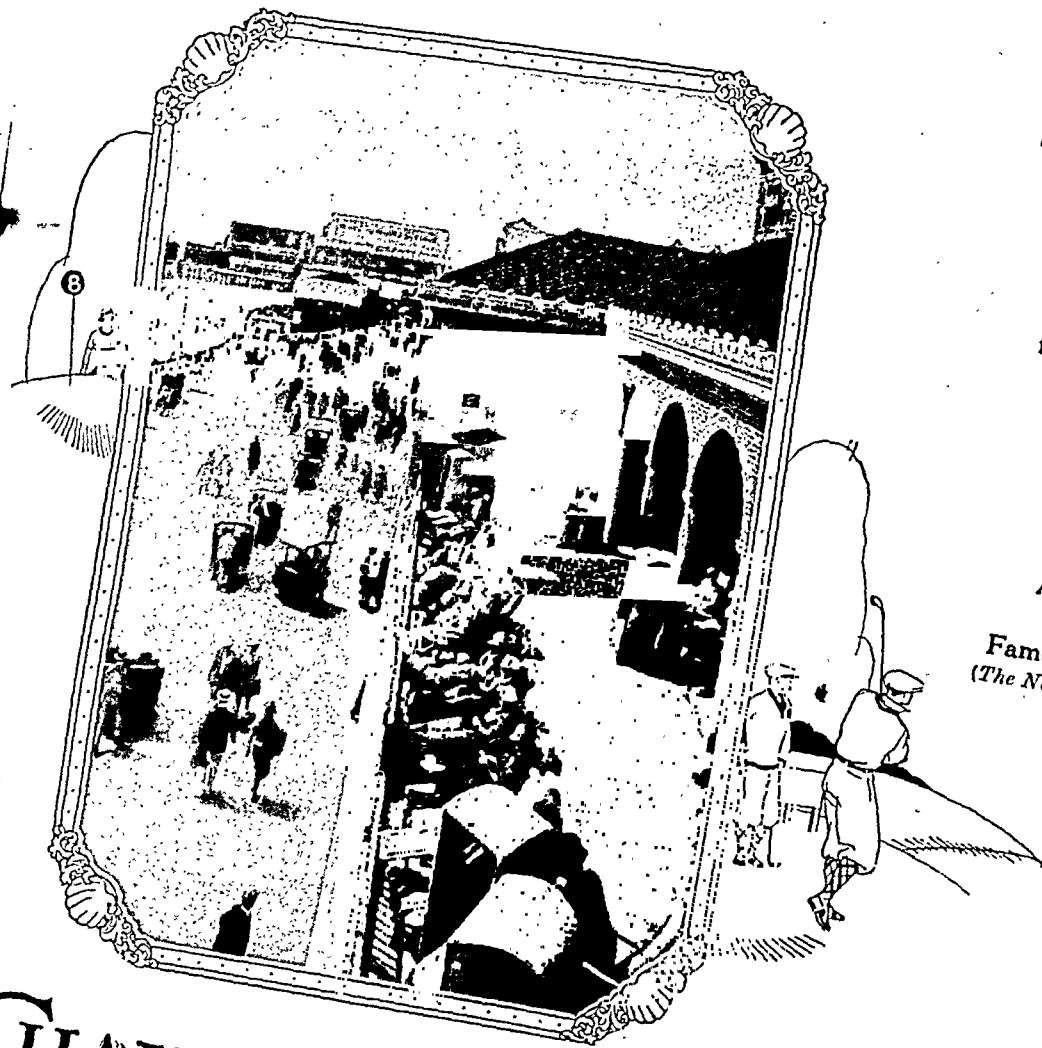
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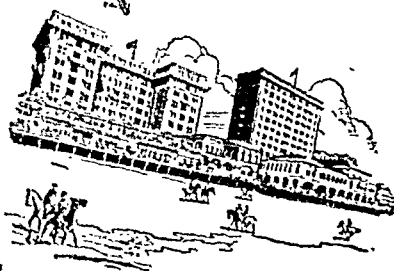
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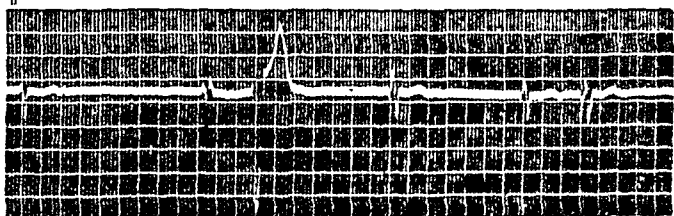
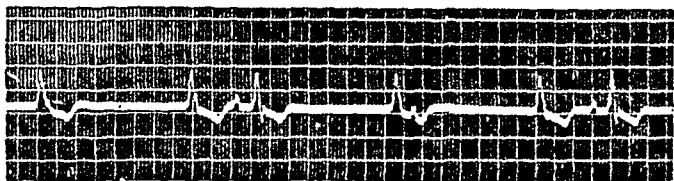
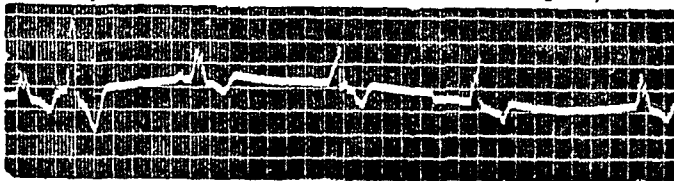
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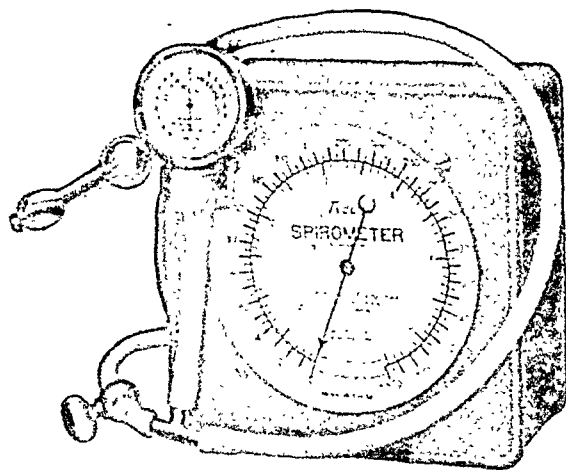
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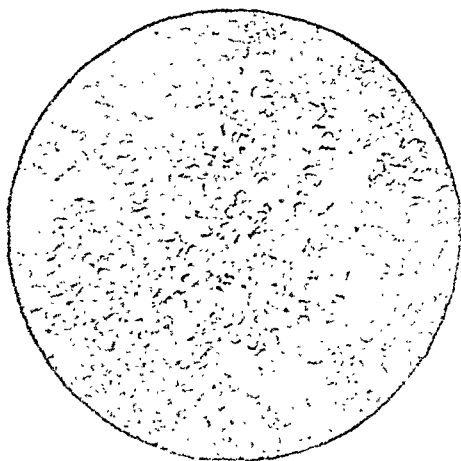
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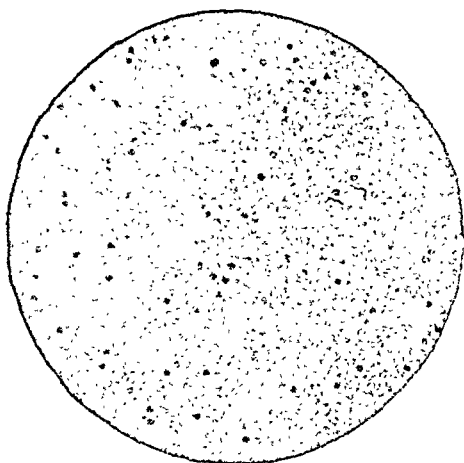


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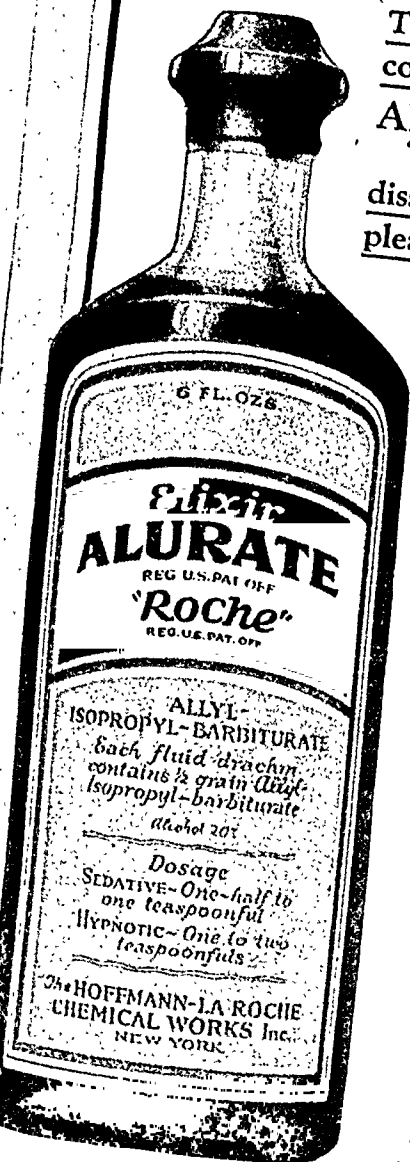
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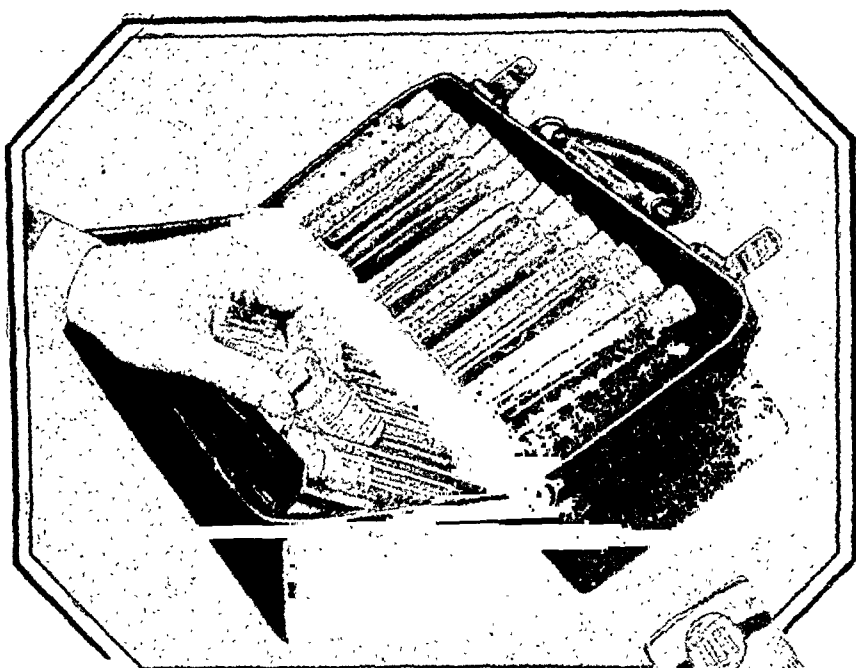
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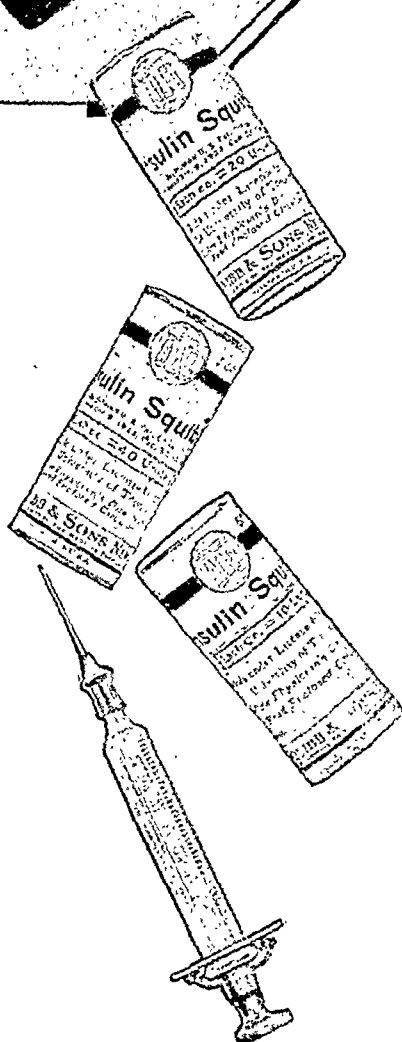
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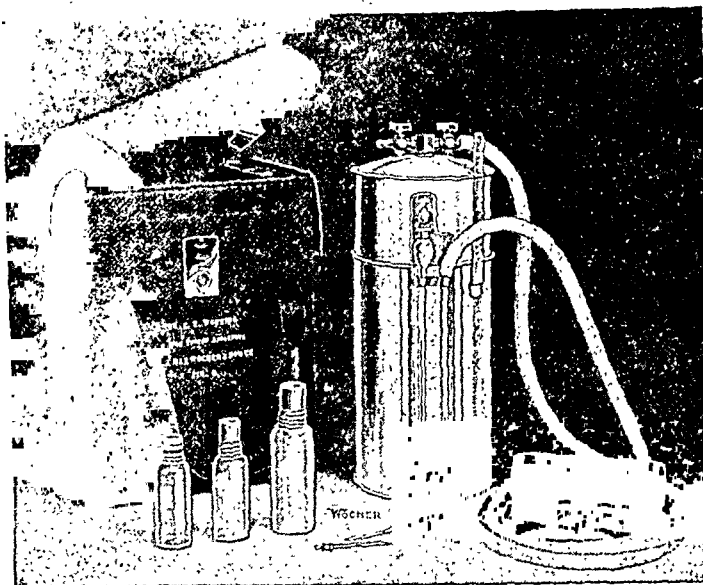


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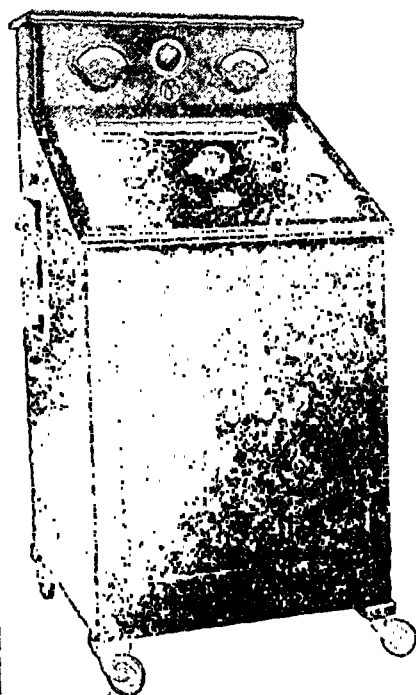
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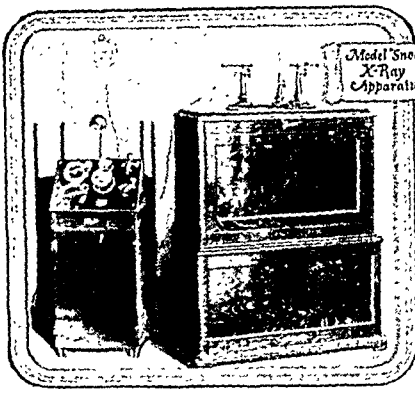
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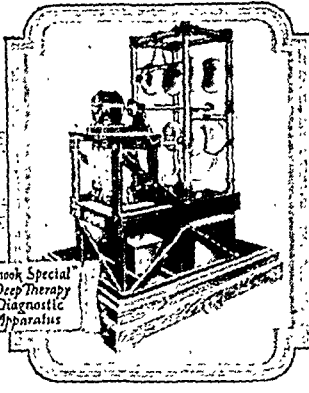
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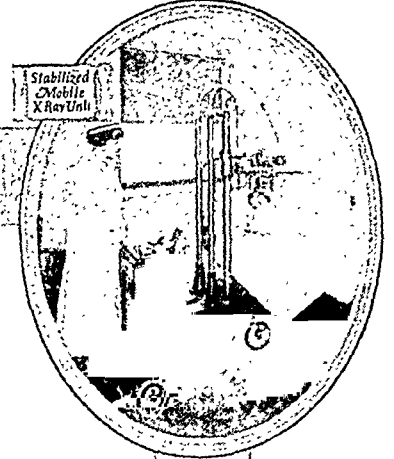
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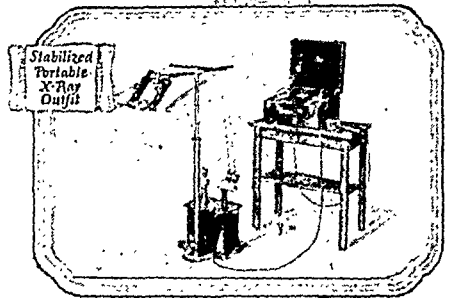
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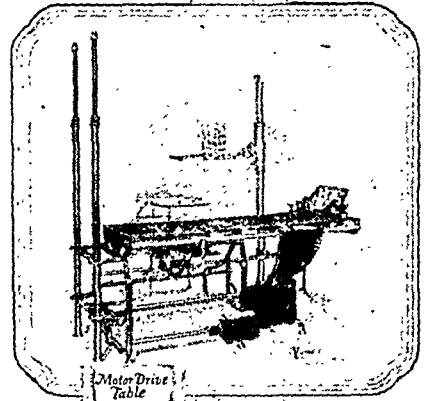
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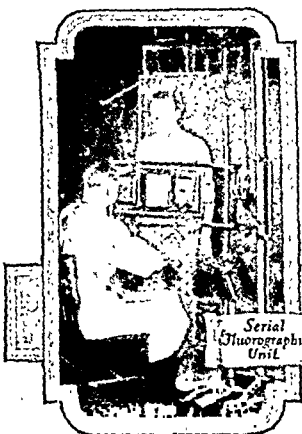
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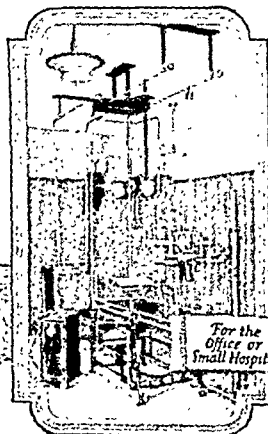
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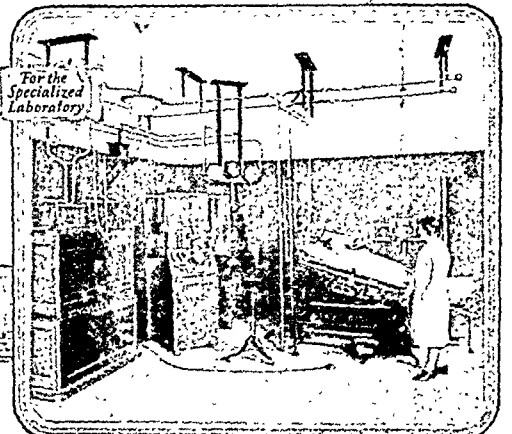
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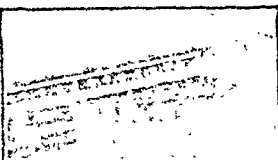
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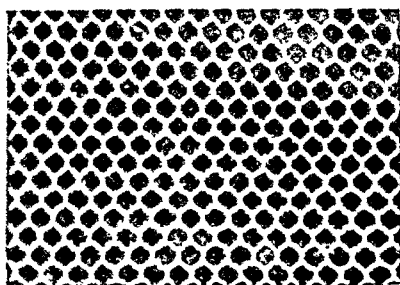
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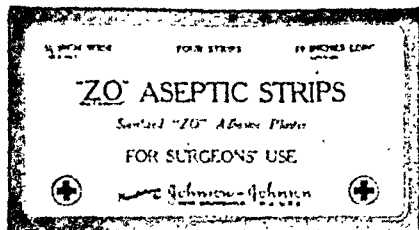
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THE
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ORIGINAL ARTICLES.

HEREDITY IN THE CLINIC.*

BY LEWELLYS F. BARKER, M.D.,
BALTIMORE.

To the biologists and especially the geneticists of this country, it must be little short of amazing that American clinicians have been so little influenced either in work or in thought by the stupendous advances that have been made in our knowledge of heredity since the turn of the century. For to the advances in genetic theory and practice, which began with the rediscovery by Johannsen in 1900 of Mendel's fundamental laws, American biological investigators have been among the most important contributors; moreover, our biological teachers and writers, too, have been busily engaged in disseminating widely the newer knowledge acquired both here and abroad. Researches like those of E. B. Wilson upon the cellular basis of heredity, of T. H. Morgan upon its physical basis in the fruit fly, of H. S. Jennings upon inheritance in unicellular organisms, of C. E. McClung upon the heredity of sex, of W. E. Castle upon blending inheritance, and of E. M. East upon inbreeding and outbreeding have yielded results that are famous the world around; methodology has been sufficiently covered by the writings of the scientists mentioned and by Raymond Pearl in his "Modes of Research in Genetics." Popular presentations, such as E. G. Conklin's "Heredity and Environment in the Development of Man," H. F. Osborn's "Origin and Evolution of Life," H. H. Newman's "Readings in Evolution, Genetics and Eugenics," and H. S. Jennings' "Prometheus" have made the main facts and theories easily accessible to any cultivated reader. Furthermore,

* Read by invitation at the meeting of the Inter-State Post-Graduate Assembly, Cleveland, Ohio, October 19, 1926.

the important recent works of foreign investigators of heredity (Johannsen, Bateson, Baur, Pearson, Punnett, Thomson, Goldschmidt) will be found available for reference in every large library. As I write, a new and important series of monographs by Johannsen, Brugsch and others is announced in "Die Biologie der Person." American biological thought is saturated with genetic considerations; they influence, too, to no inconsiderable degree, contemporary pedagogy and philosophy. Why then the apparent apathy of medical men with regard to the problems of inheritance? How can we explain the sluggishness of our clinics as far as efforts to apply the newer knowledge and technique to the solution of the problems of health and disease in man are concerned? There surely must be special reasons for the glaring contrast between the fiery enthusiasm for researches in heredity and development evident in the biological laboratories of every university and the coolness toward genetic questions and the concentration upon environmental influences that characterize activities in our hospitals and even in the laboratories of clinical research of our university medical schools.

This crass discrepancy between the biological and the medical interest in heredity has not been limited to America; it has been observable, and has already been subject of comment, in other countries. Various causes can be assigned, among them the following: (1) A temporary blindness to the significance of heredity for medicine owing to the fruitfulness of studies bearing upon environmental factors that favor health or cause disease (particularly since bacteriology, parasitology and toxicology have brilliantly emerged as sciences and since public and personal hygiene have been able to make such gigantic strides by attention to habits and surroundings alone without much consideration of endogenous determining influences within man himself); (2) the erroneous idea that for practical medicine genetic studies have only a limited application and chiefly then in domains relatively unimportant for human responsivity and accordingly for diagnosis and therapy (such as the color of the hair and eyes, the congenital malformations, and certain rarer pathologic conditions such as albinism, retinitis pigmentosa, and the heredofamilial diseases of the nervous and muscular system); (3) the mistaken conception that emphasis upon heredity and constitutional makeup are necessarily conducive to pessimism in therapy and to a paralyzing fatalism (illustrated by past and present ideas of "stigmata of degeneration," of "congenital inferiorities," of "inherited susceptibilities" to infection, to insanity, and to crime); (4) the prevalence still of the old anthropocentric view that laws of inheritance that hold for plants and animals cannot possibly be valid for man (illustrated recently in this country by outbreaks of the so-called "fundamentalists," by the passage of laws against the teaching of evolution, by the famous trial at Dayton, Tennessee, and by many sarcastic comments upon Mendelians who are sup-

posed to believe that man mendelizes like a "pea," a "Chinese primula" or a "fruit fly"); (5) finally, the lamentable general ignorance among medical practitioners and investigators, themselves, of the possibilities of application of geno-analytical methods of study to human beings, to say nothing of their total lack of training, except in rare instances, in the use of such methods (genealogical-familial, mathematico-statistical, phenogenetic, and experimental). It is, in my opinion, to ignorance, to errors, to prejudices, and to misconceptions such as those just mentioned, and others that might be cited, that the backwardness and negligence of the clinical sciences in studies of inheritance must be attributed.

Fortunately, there are signs that clinical medicine (as well as anatomy and pathology) is awakening to its new opportunities; indeed, it is probable that before very long we shall witness a flaming revival of interest in the significance of heredity for medical theory and practice. Students of eugenics have stimulated medical men to a greater interest in racial hygiene; and even ardent advocates of euthenics have begun to realize that the variable influence of their measures depends upon the innate differences among human individuals. C. B. Davenport and his associates at the Eugenic Record Office have done much to further studies of human heredity; and in the "Journal of Heredity" edited by Poponce as well as in the "Eugenics Review" (London) articles on human genesis frequently appear. Neurologists and psychiatrists, not surprisingly, have been leaders in the study of the human individual as a whole, as a psychophysical unit; they have in their studies of the relation of bodily structure to character and of general personality reactions begun to realize more fully the importance of inheritance both for body and soul. In H. H. Goddard's book on "Feeble-mindedness" (1914) detailed information is given regarding hereditary relations. In Switzerland during the past fifteen years, genealogic studies of dementia præcox and of manic depressive families have been illuminating. At the fourth annual meeting of the Association for Research in Nervous and Mental Diseases (held in 1923) the whole program was devoted to a discussion of heredity. Endocrinologists investigating the influences of hormones upon body growth, body form, and metabolism have been compelled to go beyond the hormones and to consider chromosomal constituents and their origin. [See J. Bauer on "Constitution and Endocrines" (1925).] Even internal medicine, proper, has begun to pursue systematic genetic inquiries. F. Kraus, professor of medicine in Berlin, in 1919 published (in German) a "General and Special Pathology of the Person (Clinical Correlations)." which though difficult reading, may mark an epoch in internal medicine since in it, for the first time, a distinguished professor of clinical medicine gave evidence of a comprehensive grasp of modern genetics and of the importance of the distinction between the "phenotype" or realized person and

the "genotype" or inheritance pattern from which it is derived through a series of reactions with the environment. Two years earlier (in 1917) Julius Bauer, of Vienna, had published the first edition of his book entitled "The Constitutional Disposition to Internal Diseases" in which the inherited part of the constitution, earlier emphasized by another internist (Friedrich Martius), was duly valued. In the same year, a new journal, the "Zeitschrift für angewandte Anatomie und Konstitutionslehre," began to deal with problems of the anatomy and pathology of the constitution, and soon the general and special clinics in Central Europe began to busy themselves with investigations of the human constitution in health and disease. Attempts to understand the patient, not alone his disease, began to be made; as Brugsch puts it "personalism" must be adopted as a clinical slogan. In 1923, Baur, Fischer, and Lenz published their "Human Heredity"¹ and in 1924, George Draper, through whose influence a "Constitution Clinic" was established at the Presbyterian Hospital in New York City, published his book "Human Constitution; a Consideration of Its Relationship to Disease" in which the methods he uses in studying persons as a whole are described (under the captions Anatomic Panel, Physiologic Panel, Psychologic Panel and Immunologic Panel). In May of this year the same author has published an article on "Opportunities for the Clinician and the Pathologist Offered by Study of the Human Constitution." In 1923-1924, under the auspices of the Mayo Foundation, a series of six lectures on "Our Present Knowledge of Heredity" was delivered at each of six medical schools in the Middle West, occurrences that reveal strongly the growing conviction of the desirability of rapid dissemination of a knowledge of genetics among prospective medical practitioners and investigators. In the clinical journals, articles on the "clinical significance of heredity" and on "the practical results of the study of heredity" are becoming more numerous; even in some of the clinics for the medical and surgical specialties places are being made for "specialists on heredity within the specialty!"

How absurd the misconceptions and prejudices that have delayed the application of modern genetical methods to the solution of clinical problems are when they are carefully examined! For, in the first place, instead of having a limited application to practical clinical problems, the field of possible and, in time, profitable application is as wide as those of medicine and hygiene themselves. Every human being looked at by a clinician from the standpoint of genetics is a phenotype (realized person) who has become what he is by starting as a fertilized egg cell (zygote), which arose, in biparental reproduction, from the union of a sex-cell or gamete from the father (spermatozoön) with a sex cell or gamete from the mother (ovum).

¹ Menschliche Erblchkeitslehre.

The materials of which this zygote was composed entered into reactions with oxygen, foods, and other chemical substances outside the zygote, first under the influence of the physical environment of the mother's uterus, later in the world outside. Whatever phenotype the zygote develops into (as a fetus, an infant, a child, an adolescent, or an adult) must depend, obviously, first upon the composition of the gametes that fuse to form the zygote and second upon the influences (chemical, physical, psychical) outside the zygote, which act upon it. Each gamete consists of nucleus and cytoplasm, the nucleus in turn containing chromatin threads shaped something like croquet hoops and known as chromosomes. Each chromosome consists of rows of beadlike masses that contain discrete packets of diverse chemical substances (collocations of chemical molecules); geneticists call these packets "genes." The chromosomes from the two parental gametes arrange themselves in pairs, so that each packet or gene from the paternal gamete meets in the zygote a corresponding packet or gene from the maternal gamete, the two chromosomes thus forming a set of pairs of genes. The chemicals in one member of each pair may be the same as those in the other member of the pair; more often, the chemicals though related differ somewhat in the two members of each pair; but, in any case, the genes appear to be arranged definitely in a series, like pearls on a string. The way these genes are arranged in the chromosomes in a linear manner is most important for our newer knowledge of heredity and development. In certain organisms (like the fruit fly) several hundreds of the packets have been definitely located so that topographic maps of the chromosomes and their contained genes are now available. The total aggregate of genes definitely arranged constitutes the so-called "genotypic pattern." Gradually the arrangement of the genes in the chromosomes of other organisms is being discovered; we already know something about the arrangement of genes in human chromosomes. The so-called laws of heredity have to do with the rules of distribution of genes from the father and the mother to the zygote and with the interrelations of genes belonging to different pairs within the chromosomes of the zygote. For a time, it was supposed that each gene corresponded to some particular feature in the developed organism that was spoken of as a "unit character," but later studies have shown that this was an error. It is now believed that the genes interact with one another and with the substances about them over long periods, so that the phenotypic characters that emerge are distant and indirect results of these many interactions. Thus, the red color of the eye of a fruit fly is said to be dependent upon the interaction of at least fifty genes, alteration of any one of the fifty preventing the production of the red color! Moreover, the way the genes interact with one another and with their cytoplasmic surroundings depends to a large extent upon the environment, the development that

occurs depending not alone upon the genes but also upon their surroundings to which there is never-ceasing adjustment. It must be clear then that every developed characteristic of a phenotype depends upon the genotypic pattern in the zygote on the one hand and the influences acting on that pattern from without on the other. A given genotypic pattern appears to be capable of giving rise to many different phenotypes provided it could be exposed to many different conditions during development. What an animal or a man has become depends then only partly upon the genes present at the start; the surroundings of the genes are also determining of the characteristics that ultimately emerge. No characteristic of the phenotype is independent either of the genotype or of its series of environments. Obviously then, the field for genetic studies of given phenotypes is as wide as the total sum of their manifold characteristics. The study of heredity in man is not limited to the investigation of peculiar variations or of rare anomalies and diseases; it is applicable to every detail of human structure and of human function, whether "normal" or pathologic. No less than two hundred and twenty-three heritable anomalies have been described in man already; in time many more will doubtless be recognized.

The prejudices against studies of heredity and of constitution because they are supposed to compel pessimistic and fatalistic ideas in clinical medicine is, from what I have just said, entirely unfounded. Though it is true that the genotype with which an organism starts has much to do with the development that follows, it is not wholly decisive. The limits set by the aggregate and arrangement of constituent genes certainly cannot be transcended, but the possible variations within the limits are much wider than was formerly thought. Nothing is absolutely fixed or foreordained within those tolerably wide boundaries. The genotype does determine a certain norm of reaction, but the results of reaction will differ according to the influences and substances reacted with. An organism develops through a series of successive phenotypes, each member of the series being the resultant of adjustments of the preceding member to the environment. We are learning how to change human phenotypes artificially to their advantage; that is one of the functions of medical therapy. Witness, the change in a hyperthyreotic phenotype on excision of one lobe of the thyroid, or that in a hypothyreotic phenotype on feeding thyroxin, or that in a diabetic phenotype producible by hypodermic injections of insulin! Here is room for optimism surely, for the more we know accurately of phenotypes and their origin from genotypes interacting with environments, the greater will be our power to influence them favorably. Though the "hand of the past is found to have a heavy grip" we should not forget, as Thompson has pointed out, "the other side of heredity: the persistence of the stable; the conservation of advantageous qualities; the continual emergence of the new; and the influence of nurture in

determining the degree of development to which hereditary nature attains."

The hindrance to genetic research in man because of the persistence of ancient anthropocentric conceptions will, we can feel sure grow gradually less. Medical students, today, all study general biology and, in most states, they study evolution too. As they become physicians, their biological knowledge will protect them from the fallacious idea that the laws of life for man must be wholly different from those that obtain for animals and plants. They will not be deterred from the study of heredity in man because he does not mendelize precisely as does the pea or the fruit fly, particularly when they find that man does actually mendelize.

When they find how genetic studies extend the domain of etiology to the investigation of causes that are prezygotic or progametous in the time of their influence and to researches into the origin of pathologic alterations of genes; when they learn that the genes are units fully as important for true medical conceptions as are the units known as cells, as molecules, as atoms, as ions or as electrons; when they come to understand that correlations regulated by genes are no less important than are nervous and hormonal correlations, that they are indeed even more fundamental than these; when they realize that genotypic patterns in zygotes are the keynotes to the peculiarities of all human constitutions and to the individual features of all human personalities; when they grasp the idea that no two genotypes are ever alike (except in the case of identical twins) and that every genotype, being unique, occurs only once in the world and ends with the death of the phenotype to which in reaction with environmental influences it has given rise—no fundamentalist opposition and no state or national law will deter them from views that are based on sound biology. They will be eager to participate in the discovery of as many genes as possible in human genotypes and of their influence in the production of individual human phenotypes, both normal and pathological. They will desire to learn how pathologic genes originate and how their malevolent influences can be counteracted. For they will quickly recognize that in the future of medicine studies of "gene physiology" and "gene pathology" are destined to play a very important rôle.

The technique of genetic investigation is very complex. Even genealogical and familial studies, if they are to yield reliable results, require most painstaking research. The mathematical-statistical evaluation of the findings demand a training that only relatively few have thus far gained. The analysis of human genotypes for their constituent genes and the construction of their patterns will afford work for many generations of medical investigators. To discover all the influences that a given normal or pathologic gene can exert, to learn by phenogenetic studies the relations of single genes to realized characteristics, to find out what happens to a human organism

when a gene ordinarily present is absent or altered—these are problems that are full of interest and should be stimulative of ardent research. Already important results for the clinics are being achieved, notably as regards osteogenesis imperfecta (in which abnormal genes seem to be responsible for changes in the whole mesenchyme), hemophilia (in which pathologic genes seem to be responsible for the faulty formation of thrombokinese in the body cells), and chondrodystrophia (in which changes in the growth of bone and cartilage, alterations of the physiognomy, and modifications of sexuality and of the psyche are all being led back in their causation to a faulty genotypic pattern, perhaps to a single pathologic gene).

Many have thought that heredity in man is not susceptible to experimental approach. Because human beings, genetically considered, are immensely complex "polyhybrid heterozygous bastards" and because we cannot control matings in them as we do in guinea pigs, rabbits, or garden peas, it has been assumed that experimental research can be of no value for human heredity. But no person denies the value for man of experimental research in the physiology and pathology of the heart, of the liver, and of the brain carried out on animals with cautious transfer of the results by analogy to the physiology and pathology of man. We have learned much regarding the conduction mechanism in the human heart, regarding the possible origin of cirrhosis of the liver in man, and regarding cerebrospinal localization in man from experiments on animals. Why then should we assume that genetic facts learned from animal experiment are wholly inapplicable to man. Who can doubt that researches on the heredity of tumors and of susceptibility to tumor transplantation such as are carried on at the University of Chicago, at the Rockefeller Institute in New York, and at the Wistar Institute in Philadelphia will prove to be of importance also for man? Studies in animals, too, of inherited susceptibility to various infections, to endocrine disturbances like goiter, and to various other pathologic states should all, in time yield results that can be utilized to illuminate the influences of heredity in human beings also. Disease among animals, though less prevalent than in man, occur in sufficient variety and frequency to warrant continued search for them and the study of their genotypic relationships when found. Comparative medicine can thus be forced to contribute ever new facts that can throw light on human medicine.

The subject could be pursued much further did time permit. I hope, however, that the ground already covered, will suffice to show how important a knowledge of the science of heredity and the application of its technique can be for the tasks of the clinic. As K. H. Baur has pointed out, the doctrine of endocrinology quickly conquered medical thought, largely because it harmonized with the localistic principles of the morphologists (in that the increta were

associated with definite organs) as well as with the endeavors of physiologists to study everywhere chemical reactions. The doctrines of heredity have been less congenial to medical thinkers because they were unprepared for it by their earlier education. But the younger men entering medicine today have had a better biologic training than their predecessors. And you will agree, I believe, that it cannot be long before the repercussion of the theory of heredity upon medicine will become much more noticeable than hitherto.

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ANESTHESIA FROM THE STANDPOINT OF THE SURGEON.*

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THIS paper will consist of a brief discussion of my reactions to anesthesia as judged from the experience of the past four years on

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my services in the University and Misericordia Hospitals. During that time we have had about 6000 operations, covering practically the entire field of surgery. Naturally, the surgeon is interested in anesthesia; he is responsible morally and usually legally for any carelessness in its use. He knows his patient and must select the anesthesia from such knowledge. We are accustomed to having anesthesia mostly given by a nurse trained in anesthetic methods. I cannot praise too highly the work of our regular nurse anesthetists. Their technique is wonderful, and it is surprising how much real knowledge of the action of anesthetics they have acquired from reading the standard works and periodical literature.

The particular anesthetic to be used will depend upon the operation, the condition of the patient and in the case of local or regional anesthesia the ability of the surgeon to master the technique. Ten years ago practically every major operation which I did was performed under open-drop ether anesthesia. Today the reverse is the case, ether being given much less frequently and mostly when nitrous oxid or ethylene is insufficient to afford relaxation and ether must be added. We use the Gwathmey apparatus. The following table shows the method of anesthesia used on my service in the University Hospital during the first and fourth years of the present régime:

TABLE I.

	1922-1923. per cent.	1925-1926. per cent.
Local	10	22
Ether	43	11
Nitrous oxide-oxygen	25	33
Ethylene	0	15
"Gas"-ether	17	14
"Gas"-local	2	4

The combination of gas-local, using either nitrous oxid or ethylene gas, is represented too low, because during the past four or five months we have been using novocain in the abdominal wall in practically every case of gas anesthesia. The per cent given means those cases started under local and the gases subsequently added, because of failure to anesthetize.

Local Anesthesia. Our use of local anesthesia alone has about doubled, and at the present time practically every abdominal operation is done under gas anesthesia plus extensive infiltration with novocain (0.5 per cent). One is enabled to stop the inhalation anesthesia as soon as the peritoneum is closed and the patient is conscious and talking rationally before leaving the operating room. I have had but little experience with splanchnic anesthesia, but have begun its use recently with satisfactory anesthesia, although the fall in blood pressure is rather alarming. We have used the posterior method of Kappis.

Operations for chronic appendicitis and hernia are frequently done

under local anesthesia. Inter-rib drainage of empyema and colostomy or enterostomy for intestinal obstruction are always operated upon under local anesthesia. I do not like local anesthesia alone for gall bladder or stomach operations, but prefer the gas-local combination. In this group the splanchnic anesthesia has its best application. In acute appendicitis we start the gas and drape and prepare the abdomen. Local anesthesia of the skin and muscles is then done and after the appendix is removed and drains placed the gas is stopped. I hesitate to infiltrate the mesentery of cecum or appendix, fearing the introduction of septic material on the point of the needle.

Local anesthesia has a wide application and should be studied and practised by every surgeon, so that it can be used alone or in combination in nearly every case requiring prolonged anesthesia. The anesthetic is a mental hazard for most patients, and in nearly every proposed operation, except in the case of those desperately ill, I am called on to discuss this point with the patient. Nearly every patient dreads ether, even fears it, and the discussion has been made easier for me by my ability to announce that I rarely use ether and will not do so unless forced into it. We might tell the patient that the risk in spinal anesthesia is as 1 in 500; in chloroform, 1 in 3000; while in ether it is only 1 in 16,000; but still they are not convinced. I like to operate with the patient under ether anesthesia because of the greater relaxation, the ease of exposure and the ability to "speed up." On the other hand, the ward nurses do not like it because of the frequent vomiting, the need of physical restraint in many cases and the detailing of separate nurses to watch the patient. In a ward where patients are coming down from the operating room every half hour or so this is an important item in ward management.

Ether. Ether is a safe anesthetic for the average anesthetist and for the patient, with certain exceptions. Until recent times the literature was voluminous and concerned with the technique of administration. Even now the special journals on anesthesia are mostly filled with articles bearing upon the use of ether and especially with experimental data bearing on its effects. And yet, in large clinics the use of straight ether is constantly diminishing. As has been said, the influence of the patient has had much to do with this, but there is another reason. Minor operations can be done readily under local or gas anesthesia, and the same may be said for simple major operations, such as hernia or chronic appendicitis. But the sick patient is the important one; he furnishes the mortality, that dread of all well-run clinics, and experience has taught that the prostatic, the depressed cardiorenal patient, the diabetic, the jaundiced, the patient with intestinal obstruction or acute appendicitis do not stand ether. I am not able to discuss for you the

complexities of acidosis, ketosis, ammonia disturbance, hyperglycemia and so forth. Something, however, must be known about them and certain tests carried out if we are to evaluate the risk from anesthesia.

For all practical purposes the determination of acidosis may be done by estimating the plasma CO_2 volume. The blood plasma of the normal adult contains from 50 to 65 volumes per cent of CO_2 gas as bicarbonate. If this is below 30 per cent the patient is in serious danger. Even at 40 per cent the condition is serious, and ether if prolonged will promote the production of lactic and other nonvolatile acids which cannot be neutralized. Stehle and Bourne believe that ether acidosis results from a disturbance in the phosphorus metabolism. With the increase in the hydrogen-ion concentration, the colloids of the cells will absorb water and the urinary output decrease so that further poisoning results.

In the diabetic the acidosis is generally termed ketosis, and it is well known that ether aggravates the condition by disturbing the metabolism of carbohydrates and should not be used. In the jaundice group the depressed liver loses its protein detoxicating power and the kidneys must bear a heavier burden. Ether alters and depresses the functional activity of the liver and hence should not be used to any degree in the jaundiced patient. We all know that the patient past middle age is a greater risk than the young adult, and hence the results of some very interesting experiments published by MacNider upon the stability of the acid-base equilibrium of the blood in animals of different age periods when anesthetized by ether is important. In puppies and young adult animals it was found that the physiochemical state of the blood was stable and practically uninfluenced by the ether, whereas in old adult dogs it was found that the acid-base balance of the blood was not stable. There occurred a marked reduction in urine formation, with the appearance of albumin and casts in the urine and more rarely diacetic acid; the elimination of phenolsulphonephthalein was markedly reduced. Even anuria occurred. It seemed that the kidney was furnished a blood of such altered composition that it failed to functionate in a normal fashion. Barbour and Bourne, of the department of pharmacology, McGill University, believe that ether oliguria and anuria are probably due more to thickening of the blood than to any renal factor. They found that the preanesthetic administration of water or hypotonic solutions reduces markedly the blood concentration produced by ether.

We spoke of vomiting as a postoperative trouble from ether. On the second day the patient experiences certain pains which are traditional as the inevitable "gas pains." Many remedies have been suggested but I believe the anesthetic itself is the important factor. This is confirmed by a paper recently published by Miller,

from the department of pharmacology, State University of Iowa. He found that after ether or chloroform anesthesia the stomach remained relaxed, whereas the small intestine early shows exaggerated peristalsis; the colon soon after anesthesia is withdrawn develops a high tonicity which may approach spasticity. This high tonicity of the colon acts as a functional, partial obstruction, favors the accumulation of gas and fluid above this level and the exaggerated peristalsis of the small intestine above the partial block could cause the so-called "gas pains." On the other hand, the usual anesthesia with ethylene and oxygen produces relatively little effect on the movements of the gastrointestinal tract, no inhibition of tone or of contractions occurring with this form of anesthesia. Tone is lowered, peristalsis ceases and segmental contractions are much diminished. This depression usually lasts one hour or longer.

Pulmonary Complications. The so-called ether bronchitis or ether pneumonia is stressed by many surgeons in explaining the reason for these complications to the relatives of the patient. If a patient, not in an acute stage requiring immediate operation, is operated upon while suffering from a cold the surgeon can expect trouble and is responsible for it. But in the average case the ether itself has little influence upon the development of pulmonary complications. From September, 1925, to September, 1926, 1132 operations were done on my service in the University Hospital, and there were 12 pulmonary complications (1.1 per cent). The anesthetics used in these cases were ether, 2; nitrous-oxid ether, 1; nitrous oxid, 2; ethylene, 1; local, 2; nitrous oxid local, 2; ethylene local, 2. This was a percentage of 1.4 for the ether cases, 0.9 for the local anesthetics, 0.7 for ethylene and 0.6 for nitrous oxid. After inhalation anesthesia alone (ether, nitrous oxid or ethylene) the percentage of pulmonary complications during this year was 0.9 per cent, whereas when local anesthesia was used, with or without combinations (with ether, nitrous-oxid oxygen or ethylene) the percentage was 2.2 per cent. One of the ether cases followed endotracheal anesthesia resulting in multiple lung abscess. I do not like this form of anesthesia but was asked to use it.

Recent writers, especially Cutler and Hunt, believe that except for acute bronchitis the pulmonary complications are mostly due to emboli. Hence rough handling of tissue and the crushing of large veins is as important as the anesthetic. The high incidence after local anesthesia may be due to the production of thrombosis in veins injured by the needle puncture.

Recent studies on atelectasis of the lung tend to show that hypostatic congestion following the collapse may be converted into a pneumonia by bronchial infection. The atelectasis or collapse need not be total or "massive," but may be partial in a lobe. This may be a cause of postoperative pneumonia.

TABLE II.

	Operations.	Pulmonary complications.	Per cent.
1922-23	844	12	1.4
1923-24	1076	9	0.8
1924-25	1021	13	1.3
1925-26	1132	12	1.1
Total	4073	46	1.1

During the four years from September, 1922, to September, 1926, we had 4073 operations on my service in the University Hospital and had 46 pulmonary complications (1.1 per cent), with a mortality of 37 per cent. This constituted about 10 per cent of the mortality of the service, and hence is a factor to be reckoned with. Naturally most of the patients probably would have died from their disease, but the difference between the pulmonary group (37 per cent) and the mortality in those without pulmonary complications (3.8 per cent) shows the importance of this factor.

TABLE III.

	Cases.	Deaths
Acute bronchitis	10	0
Bronchopneumonia	15	7
Lobar pneumonia	6	3
Pulmonary embolus	11	4
Lung abscess	3	3
Massive collapse	1	0

In a study of this subject by Ravdin and Kern from our hospital it was found that seasonal variation, incidence of subnormal temperature after operation, sex and age, location of the ward and duration of anesthetics, all played a part. If to these we add the still greater factors of small emboli and partial atelectasis, we see that the anesthetic alone must not be held responsible if we exclude the important factor of an existing "cold" antecedent to inhalation anesthesia.

Nitrous Oxid and Ethylene. For many years nitrous oxid and oxygen have been used in our clinic, and its use was gradually extended, until last year 33 per cent of the operations were done under this anesthesia. When ethylene was brought out, and especially after Dean Lewis popularized its use, we began using it. Last year 15 per cent of the anesthetics were by ethylene, making a total of 48 per cent for the "gases." I will not dilate at any length upon these anesthetics except to say that our anesthetizers start with nitrous oxid; if relaxation is not soon attained they switch to ethylene and if the patient is still unrelaxed they add ether to the gas mixture. In about 30 per cent some ether was necessary. At the present time the addition of ether is rarely necessary, owing to the combination of local anesthesia with gas as a routine in abdominal operations. I know of only one death that might be traceable directly to gas anesthesia, a case of intestinal

obstruction from a gall stone, the patient dying suddenly on the table from cardiac failure. Once I had a similar death under spinal anesthesia, once under local anesthesia and several times from ether:

Leake, of the University of Wisconsin, concludes that: "Ether causes: (a) An immediate and marked fall in both the blood pH and bicarbonate, leading, if the etherization is sufficiently prolonged, to an uncompensated alkali deficit; (b) this response is independent of respiratory variations under the influence of ether, and is not caused by the formation of ketone bodies nor lactic acid; (c) there may be a ketosis developing several hours after the withdrawal of ether, due probably to deranged carbohydrate metabolism, which is apparently related to the depressing effect of ether on the normal insulin secretion of the pancreas."

Nitrous oxid and oxygen anesthesia necessitates some degree of anoxemia, and this is responsible for certain changes which are, according to Leake, "an initial increase in the pH with inconstant changes in the CO_2 content." The reaction is not as marked as after ether.

The effects of ethylene-oxygen anesthesia on the blood reaction were found to be even less than after nitrous-oxid oxygen, because it is possible in most cases to keep the oxygen saturation of the arterial blood within normal limits and hence there is no anoxemia. If anoxemia is present Leake finds that: "There is an initial mobilization of blood alkali, followed by a gradual tendency toward an uncompensated alkali deficit. If no anoxemia is present the pH and CO_2 content of the blood both fall gradually, but not beyond normal limits after forty minutes' anesthesia."

I would also call attention to the fact that local anesthetics, unless used in toxic doses, have no effect on the blood reaction.

Cases with high blood pressure and poor cardiac risks are ordinarily excluded from gas anesthesia. In the former we prefer local anesthesia or, if necessary, ether if the kidneys can be protected. In cases with a poorly compensated heart lesion local anesthesia should be used and care taken regarding the depressing effect of the preliminary morphin dose.

Cardiac Factors. We are rarely afraid, however, of the cardiac factors in deciding upon anesthesia. The patient and his family physician worry a lot about the condition of the heart and frequently I have had to combat the statement, "My doctor says I should never take ether because of my heart." Many murmurs are purely functional, and even the organic leak or stenosis causes no anxiety if compensation is present. Auricular fibrillation requires study and preoperative treatment. The use of the blood pressure apparatus and renal function tests are of paramount importance in eliminating or minimizing the cardiorenal impairment. Naturally one would not operate needlessly upon a case of angina pectoris.

Kidney Factors. More important than the heart is the condition of the kidneys. Without going into the theoretical aspect of the question, I find it advisable to know certain things about kidney function in all patients past middle age and to watch this function in all sick patients before and after operation. Intake and output charts are invaluable, blood urea and nitrogen tests, and in the ordinary urinalysis the search for pus or blood cells in the urine is routine with us. I think that blood pressure determinations are valuable because an adequate maintenance of the pressure is essential to both glomerular and tubular activity. All of the changes in the rate of renal secretion, which occur in individuals whose kidneys were functioning normally previous to operation, can be explained as the consequence of a rise or fall of the blood pressure and of a simultaneous variation in the velocity of the blood in the renal vessels.

Richards and Schmidt, of the University of Pennsylvania, have demonstrated that the glomeruli of the frog's kidney have periods of constricted closure alternating with periods during which they permit the flow of blood. Although this introduces a new factor into the problem of urinary secretion, it is conceivable that in individuals whose blood pressure has dropped considerably below the preoperative level the resulting circulatory stasis produces in effect a continued glomerular constriction. No doubt you are familiar with Mott's rule, which is supposed to furnish an index of one phase of the anesthetic risk. It is based on the relation of pulse pressure to diastolic pressure. It reminds us that pulse pressure, as an indication of cardiac strength, must be sufficiently high to compensate for a deficient kidney function because the addition of fluids is useless if the pressure cannot push them through the kidneys. We find that ordinarily glucose solution given intravenously is a better diuretic than the drugs, such as caffeine, which are so often used.

I do not need to caution you of the danger of ether in operations on the chronic prostatic. Local anesthesia and ethylene, parasacral anesthesia, or even spinal anesthesia, have the preference. The age of the patient, the susceptibility to respiratory complications and the surety of some degree of kidney damage are sufficient reasons.

General Considerations. The physician or surgeon must not be led into ascribing an undue importance to the action of the anesthetic agent. Clinical experience and even pharmacologic investigation show the relative harmlessness of anesthetics properly given in the young adult who is not toxic. Many of you no doubt use ether as a routine and can point to your series of successful operations, but I am sure if you card index your patients suffering with diabetes, jaundice, depressed kidney function, toxic goiters, hypertrophied prostate and acute appendicitis, and study the deaths you will note that usually they die from an aggravation of the lesion existing before operation. If you will properly study these patients,

properly prepare them, use local anesthesia to the limit and follow up the postoperative treatment with "floods" of water you will find that in the next series the mortality will be cut enormously. The principle of anociassociation, devised by Crile for the toxic goiter patient, is applicable to all and we must never minimize in our minds the inherent fear which the patient has of operations and anesthesia, and the drive of this fear on the central or sympathetic nervous system.

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SUMMARY OF EXPERIENCES UP-TO-DATE IN THE SURGICAL TREATMENT OF ANGINA PECTORIS.*

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THE surgical treatment of angina pectoris is based on the hypothesis that the stimuli which give rise to the symptom pain arise in the heart and are carried by some nervous pathway to the spinal nervous system where these impulses overflow and stimulate the somatic sensory neurons supplying the upper thorax, arms and neck. The surgical act is aimed at division of this nervous arc, thus preventing the patient from recognizing the symptom pain. As the pathologic condition which causes angina pectoris is still unknown, there is no intention of eradicating the disease by surgery. It is a method of treatment which is purely symptomatic, and therefore identical in purpose with the division of the sensory root to the Gasserian ganglion in cases of trifacial neuralgia.

The operative treatment of angina pectoris was first proposed in 1899 by François Franck. It was first practised by Jonnesco in 1916. The operation performed by Jonnesco was an elaborate procedure, as he felt it was necessary to remove completely the upper three cervical ganglia and the first dorsal sympathetic ganglion on both sides. Chiefly because of the technical difficulties and in spite

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of the fact that Jonnesco's first case presented a most satisfactory result, the operative treatment of angina pectoris was not popularized. In 1923, Coffey and Brown, of San Francisco, claimed that their experience on 5 cases showed that removal merely of the superior cervical sympathetic ganglion or even division of the main branch from this ganglion to the heart sufficed to ameliorate the pain in cases of angina pectoris. The successful results reported by these investigators using such a simple procedure led to a very general practice of surgical operations upon patients suffering with angina pectoris. Whether the procedures above mentioned or the many variations of them, or even the division of those branches from the vagus nerve thought to be the depressor nerve, are of value in the treatment of angina pectoris is still under dispute. Even if these procedures fail ultimately to prove of great practical value in clinical medicine, the stimulation toward the study of cardiac pain and the proper innervation of the heart will have been of great value to the profession. It is perhaps unfortunate that a certain phase of this endeavor could not be studied experimentally in animals, but here, as in comparable instances in medicine where pain is the chief symptom, we must conduct our final investigations upon human beings themselves.

Before we turn to a discussion of the results achieved by the many varied procedures proposed in an effort to see which procedure has been most successful in abolishing the symptom pain, we must orientate ourselves by an appreciation of the nervous connections of the human heart. Figure 1 shows schematically the general relationships. The total innervation of the heart is comprised in the paired vagi and sympathetic nerves. Physiologic experimentation in which these nerve trunks and their cardiac branches have been completely divided prove beyond doubt that there are no other nervous connections between the heart and the central nervous system. Similar isolation experiments involving only one or the other pair of nerves or experiments with incomplete separation of the total nerve supply have given us definite information concerning the functions of these nerves. It has long been known that certain of the vagal fibers constitute the so-called depressor nerve, and it is known that in this nerve are afferent fibers and that stimulation of the central cut end will slow the heart beat. These are the only fibers in the cardiac portion of the vagus system which are afferent. As regards the sympathetic nervous connections, we have equally constant and accurate information. It is possible to trace histologically sensory fibers in the sympathetic system, and investigators have proved that some of these sensory fibers in the sympathetic connections run up from the heart as high as the middle cervical ganglion. No sensory fibers, however, have been found above this point, and we may be certain that the superior sympathetic ganglion and its branches have a purely motor function. These sensory

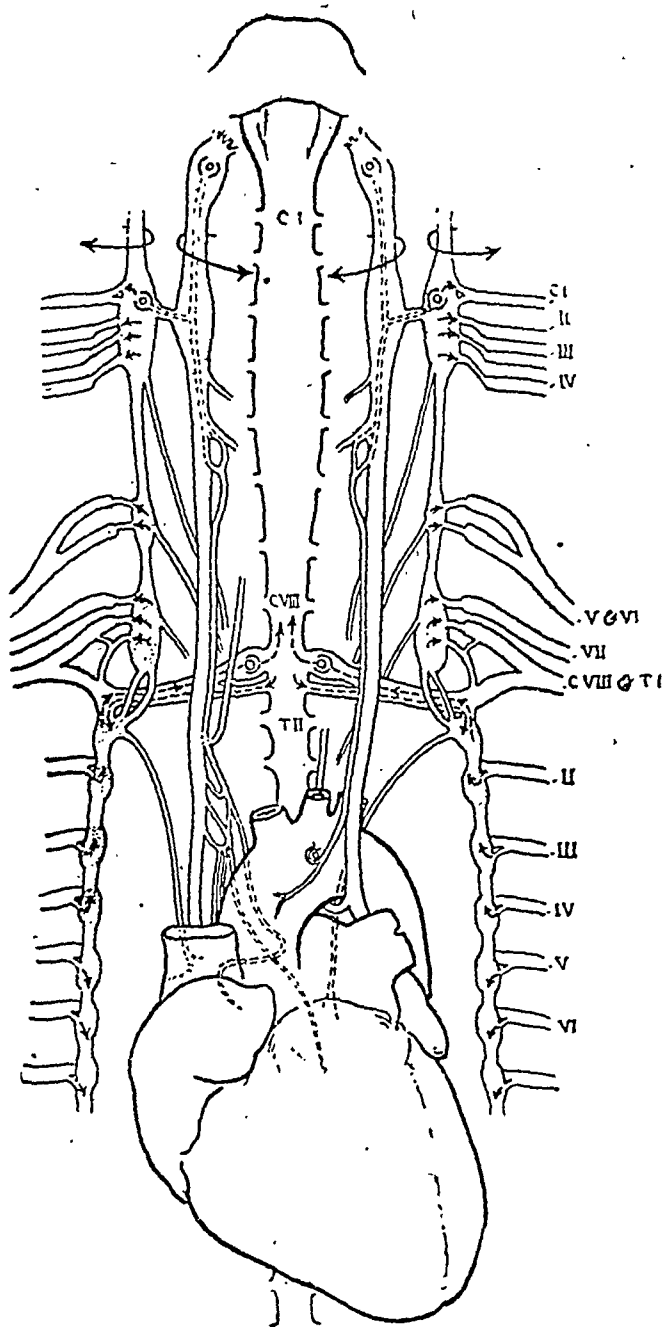


FIG. 1.—Connections of the heart with the central nervous system. The paired vagi are shown next to the cord with the ganglionated sympathetic chains external to the vagi. The connections of the sympathetic ganglia with the spinal nerves are drawn in. The origin of the depressor nerve in the superior sympathetic ganglion and in the upper ganglion of the vagus are represented with these fibers drawn in with dashed lines in the vagi and sympathetic ganglia. These fibers then branch away with the superior laryngeal nerve and finally travel free in the neck to end in the suprasternal portion of the aorta. The fibers running from the three cervical sympathetic ganglia medially and downward represent structures commonly called the upper, middle and lower cardiac nerves. These nerves are joined by many vagal fibers and fibers from the stellate and sometimes second dorsal ganglia to form a great network both in front and behind the aorta and base of the heart, in which in turn are embedded many sympathetic ganglion cells. Except for the connection of the vagi with the central nervous system in the brain stem, the connections between the stellate ganglion and the spinal cord at the level of the first dorsal nerve represents the only proved connection between the heart and the central nervous system.

sympathetic fibers, whether reaching primarily the middle or the inferior cervical sympathetic ganglia or the stellate ganglion, eventually end in the stellate ganglion from which emanate direct sensory fibers leading to the spinal cord. There is no such spinal connection above this level. The confirmation of this work, which was originally studied by Langley and Gaskell by degeneration experiments, has been recently given by Edgeworth and Ranson. In the illustration the paired vagi and sympathetic nerves are represented beside the spinal cord. The recurrent nerves are seen coming off the vagi which lie next to the spinal cord, and finally branches either from the recurrent or from the lower limits of the vagi in the cardiac area are seen coursing toward the heart. These may be said to represent schematically the depressor nerves which carry the only sensory vagal fibers. Coming away from each sympathetic ganglion, we have represented other branches. In sequence from above downward these are called the superior, middle and inferior cardiac nerves. We have then to consider as possible nerves which should be cut in stopping the reference of stimuli from the heart to the central nervous system only the depressor nerves, which are of vagal origin, and the nerves from the heart which reach to the lower and middle cervical ganglia as well as to the first thoracic or stellate ganglion.

The original operation of Jonnesco included the removal of the cervical sympathetic ganglia on both sides from above downward, including the first thoracic ganglion. In view of our present knowledge, this would seem to remove all possible sensory lines of communication to the central nervous system except the depressor fibers. The proposal that the sensory impulses in angina pectoris might be carried to the central nervous system by the depressor nerve was made by Wenckebach, and certain surgeons have attempted to interrupt these lines of possible sensory communication. It is very doubtful whether the depressor nerve can be identified in an operative procedure. The only sure method of finding it would be to stimulate all fibers found in a certain region in the neck and study the effect upon the heart rate. This nerve is known by the anatomist to have a very variable course, and it is most unlikely that it could be identified with regularity in human cases. Furthermore, there is no reason to think that it carries stimuli which might result in the pain that occurs in angina pectoris. In the first place, stimulation of its central cut end does not produce the somatic reactions of rise in blood pressure and heart rate, sweating and emotional disturbances either in man or animal which one might expect if it could carry such impulses. In the next place, its point of central connection is in the region of the medulla and an overflow of stimuli here would hardly be recognized as pain in the brachial and thoracic region which is the usual location of the pain in the clinical disease, angina pectoris.

It is certain that if we consider angina pectoris as a cardiac disorder, we must imagine that the stimulus which ultimately results in pain arises in the heart. It is true that the pain in angina pectoris usually is present in the arm or upper thoracic region. This would seem to mean, if we accept the modern view of referred pain, as proposed by Head and Sherrington, that nonspecific impulses enter the spinal cord, and because of their intensity overflow and stimulate the sensory nerves in that region, so that in the case of angina pectoris the impulses must reach the spinal cord in either the lower cervical or the upper dorsal segments.

With this in view, let us turn to a review of what has happened to the patients who have been submitted to ablation of either the vagus or sympathetic pathways. For convenience of study we have divided them into the following five groups:

TABLE I.

GROUP I. The complete Jonnesco operation.

- A. Bilateral.
- B. Unilateral L or R.*

GROUP II. Operations upon the cervical sympathetic chain.

- A. Superior cervical ganglion procedures = either excision of ganglion or division of superior cardiac nerve, or A' of the ramus communicans, that is, main connecting trunk.
- B. Middle cervical ganglion procedures = either excision of ganglion or division of middle cardiac nerve, or of the ramus communicans below ganglion.
- C. Inferior cervical ganglion procedures = either excision of ganglion or division of inferior cardiac nerve, or of the ramus communicans below ganglion.

GROUP III. Operations upon the depressor nerve.

GROUP IV. Combined operations, atypical, upon both the vagus and sympathetic elements.

GROUP V. Procedures aimed at the posterior nerve roots themselves.

*L or R = left or right sided.

Group I concerns the complete Jonnesco procedure, which consists in removal of the complete cervical chain down to and including the first thoracic ganglion. This group is subdivided into the classes in which the operation is completed on both sides or only upon one side.

Group II is that group into which we have arbitrarily placed all the partial cervical sympathetic procedures. These are further subdivided according to how much of the cervical sympathetic apparatus has been removed. There is the greatest variation in this group, but it is well to mention here that operation from the middle cervical ganglion down should have a quite different significance from those operations which concern solely the upper cervical ganglion and its ramifications. We have pointed out that the function of the upper ganglion is purely motor whereas we know sensory fibers run through the cervical sympathetic system, beginning as

high as the middle ganglion and including the first dorsal or stellate ganglion.

In Group III we have placed the various operations, unilateral or bilateral, upon the depressor nerve, and these constitute the only interference with the vagal system.

Group IV includes a few combined operations in which both the vagal fibers as well as the most varied group of sympathetic fibers have been divided.

Group V concerns procedures which attack the posterior sensory nerve roots. In some of these cases novocain or alcohol was injected into the dorsal ganglia; in others the roots were actually cut.

In Table II we have summarized the results in 120 cases selected from the literature. We have included in this analysis of the material available probably only a small fragment of the cases which have actually been performed. This is partly because certain of the data are so meagerly presented that they cannot be of value. Certain cases, in which it was obvious that the procedure was performed mistakenly for other diseases than angina pectoris, have been discarded. Certain authors, notably Leriche, who has stated that he has performed as many as 80 cases, have never presented their complete material in published form. Reasonable doubt can unquestionably be cast upon the final diagnosis in some of the cases used for this summary, and still further doubt may be cast upon the results as tabulated by the various surgeons. We have frequently found in articles that in summarizing his report the author has stated that all cases were relieved, and yet in the intimate case reports of the patients as appearing in the same article one finds such statements as, "the patient continues to take small amounts of nitroglycerin" or "the patient still complains of considerable retrosternal distress." In view of the fact that there may be a psychic element in the clinical disorder, angina pectoris, it is extremely hard to correctly classify the end results, for it is possible that quite unintentionally by holding out hope to the patient the surgeon may have done an amount of good which he has translated as an operative result. The material available, however, is sufficient to allow certain deductions to be drawn, and, although in reading the reports of cases one can never be absolutely sure that the patient submitted to operation had angina pectoris, it is most probable that the great majority of those included in this series actually suffered from this disorder.

A study of this material brings home the deep impression that it is unfortunate that surgeons should explore any fields in the diagnosis of which they may not be sufficiently expert. There is no diagnosis in medicine which requires greater discrimination than the diagnosis of angina pectoris. Since the cause of the disease is unknown, the clinical picture alone can be used in classifying

cases. The clinical picture of angina pectoris closely simulates that presented by many cases of aortitis, of aneurysm of the aorta and of infarct of the heart. There may be those who believe that coronary disease is synonymous with angina pectoris, although there is plenty of evidence in cases which have come to autopsy, including the first case described by Heberden, that coronary disease may frequently be absent in patients suffering with the typical pain of angina pectoris, and in whom relief was given by the administration of nitrites.

The figures presented in Table II show that 62 per cent of the patients submitted to the Jonnesco procedure, both unilateral and bilateral, are in a satisfactory condition for a sufficiently long period after operation to justify the assumption that the operation has benefited the patient. In addition to this large percentage, 18.5 per cent have been improved. This means that 80 per cent of the patients submitted to this procedure have been improved. If we take the various procedures upon the cervical sympathetic chain as a whole, we find that 41.5 per cent of the patients are certainly relieved following the procedure and that an additional 35.8 per cent are improved. The total figures for Groups I and II show that roughly around 80 per cent in each group seem somewhat relieved. When one intimately surveys the individual cases in these two groups, it is obvious that *the results by the complete Jonnesco procedure are better than those given by the simpler procedures involved in any of the cervical sympathectomy operations*. The Jonnesco procedure, however, gives a slightly higher operative mortality. It is interesting to note that all the fatalities in this group occurred following the unilateral procedure, but this probably means that the patients who were not good risks found the one-sided procedure too great, and any patient who could survive the risk of operation—and this probably means the risk of any operation—would survive a second procedure on the opposite side.

In view of the discussion above concerning which pathways were interrupted in the various operations, it would be well to compare the figures for superior cervical sympathectomy with the other procedures, for in this operation we are concerned only with motor pathways. In operations involving the superior cervical ganglion or the superior cardiac nerve we find that only 34.5 per cent gave a good result, and that only 72 per cent were improved by the procedure. This does not contrast favorably with the results achieved by the Jonnesco procedure where 62 per cent were good results and 81 per cent were improved. *It appears from these figures that interrupting motor pathways is not so satisfactory a method of blocking the painful attacks in angina pectoris as interference with pathways which we know are sensory in function*. It is certain, however, that in some cases where the sensory pathways were blocked, and where only the superior cervical ganglion remained, that anginal attacks

have recurred with the radiation of pain into the face and neck, which is the area supplied by the superior cervical ganglion. This would indicate that the motor element is a factor in some cases of angina pectoris.

The operations in the depressor group are too few to draw any conclusions from, as are the combined operations in the depressor and cervical sympathetic group. Moreover, one can justly cast some doubt on the fact that the depressor nerve was actually cut in these procedures. If it was not cut the fact that some relief has been obtained gives us reason to again bring up the question as to how great the psychic element is in the clinical disorder, angina pectoris.

At this time we do not feel that it is justifiable to discuss procedures upon the posterior nerve roots. It seems possible that by destroying these roots, either with alcohol or by operative methods, the nervous arcs would be interrupted which allow the patient to perceive the symptom pain. The material presented, however, by those investigators interested in this procedure is not convincing. Certainly many of the patients did not suffer from angina pectoris, although there is no doubt that they had precordial pain. Again the relief is a temporary matter where novocain or alcohol is used, and, as a further consideration of this group, we feel that the injection of alcohol into the posterior nerve root, though possible, may not be such a safe procedure as its simplicity would seem to indicate. Things accomplished in surgery unaided by vision, or the use of a powerful drug like alcohol, and particularly when in proximity to the delicate structure of the nervous system, are often fraught with grave danger and entail serious consequences. The fact that relief can be obtained by such a method does not make us feel that this is the best way to obtain it.

Conclusions. It would seem that a sufficient number of cases have now been presented to draw certain deductions. From these figures it appears that operations which divide the known sensory pathways in the sympathetic nervous system connecting the heart with the central nervous system give a fairly high percentage of satisfactory results. It is apparent also that the complete Jonnesco procedure achieves part of its success because it interferes with a motor autonomic reflex as well as interrupts the sensory pathways. Whether this operation is unduly extensive, as proposed by Daniélopou, and whether division of the sensory elements entering and leaving the two lower cervical and the first dorsal ganglia, but without removal of the ganglia, will yield more satisfactory results is still to be proven. The failure of any single procedure to alleviate the pain in all cases leaves us with the definite impression that much more is to be learned. If the division of a certain pathway eradicates the pain in one case, why should it not do the same in every case? The fact that it does not, and the fact that so many varied pro-

cedures give relief one time and again fail, arouses more strongly than ever our curiosity as to just what it is that results in the clinical picture, angina pectoris.

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CARCINOMA DEVELOPING IN THE PAROTID (STENSEN'S) DUCT.

WITH CLINICOPATHOLOGIC REPORT OF A CASE.

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THE common pathologic conditions primarily affecting and involving the salivary ducts include the various types of infection, calculus formation and the lesions resulting from their association with each other. The usual complications and sequelæ of salivary concretions are obstruction, retention-cyst production and occasionally, following rupture of a sialoceles, fistula formation. Chronic inflammatory changes, as a rule, are evident, and often are present to such a marked degree in both the duct and gland that the basic condition is masked beyond recognition. Secondary glandular enlargement, with accompanying pain, also may obscure the picture by diverting attention to the gland, instead of the duct.

Very little information is available concerning the neoplasms of the salivary ducts. The term "tumor" is often used in the sense of swelling resulting from stricture, obstruction, and inflammation, but references to "new growths" are very uncommon. From the occupational point of view, the pneumatocoles, occasionally formed in the parotid ducts of professional blowers, are interesting. Sênèque¹



FIG. 1.—Dental roentgenogram showing shadows that were interpreted as representing areas of calcification in the nodule.



FIG. 2.—Photograph of sectioned specimen. Note tightly-fitting capsular structure about nodule. The mouth of the parotid duct is recognized by the attached tag of buccal mucosa. The hole in the center of the nodule is a needle puncture.

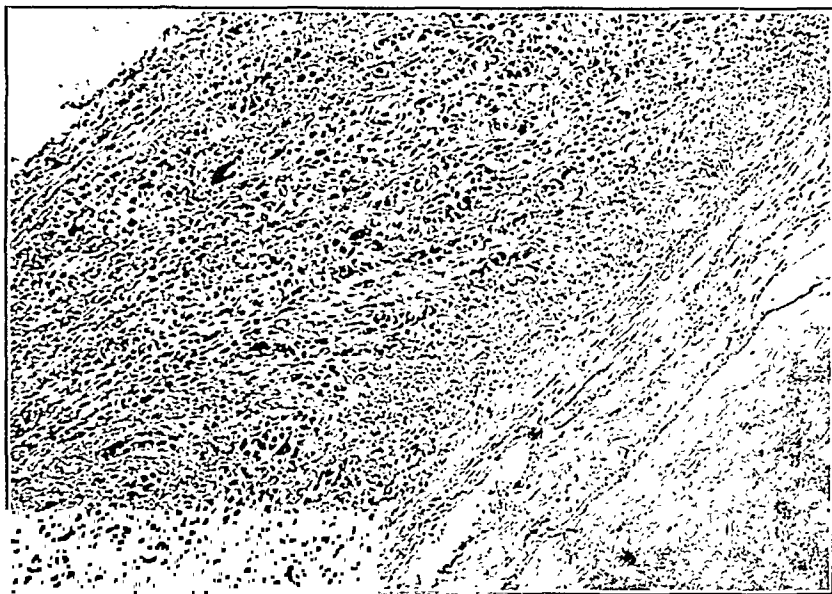


FIG. 3.—Low-power microphotograph (126 X) showing cancer cells invading the soft tissues about the nodule. Note fibrohyaline nature of the nodule with numerous areas undergoing calcification.



FIG. 4.—Low power view (126 X) showing small nests of cancer cells that have invaded the fibrohyaline portions of the nodule. An area of calcification is present.

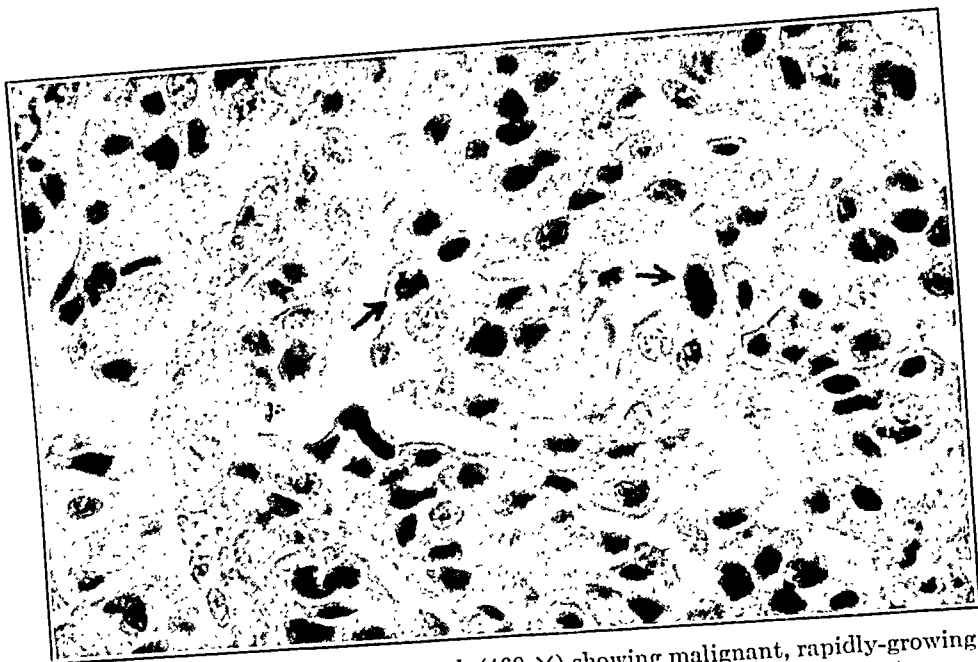


FIG. 5.—High-power microphotograph (460 X) showing malignant, rapidly-growing, anaplastic, squamous epithelial cells; the arrows point to cell-division stages.



FIG. 6.—Low power view (126 X) showing metastasis to cervical lymph node. The structure is a reduplication of that noted in the primary growth.

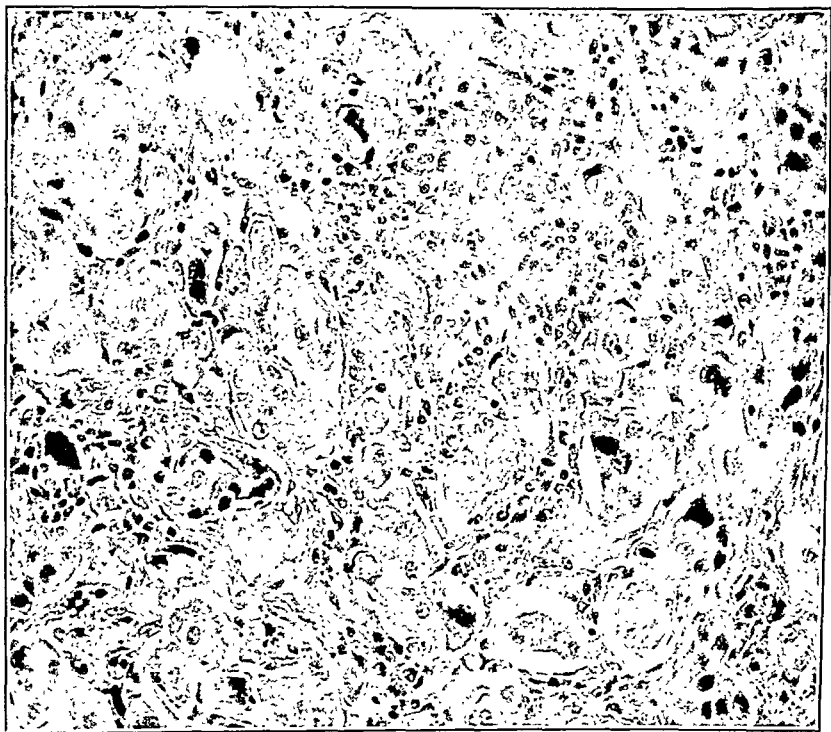


FIG. 7.—High-power view (276 X) of metastasis to cervical lymph node. The cells are quite similar to those composing the primary growth.

reports such a case with an associated multilocular retention-cyst occurring in a glassblower, and refers to other similar cases. A search through the scanty literature on the subject indicates that instances of malignancy occurring in a duct, either primarily, or in association with salivary concretions, are quite rare. Harrison,² in a recent contribution, finds that 375 cases of salivary calculi have been recorded since 1825; there is no mention of malignant disease occurring in connection with, or as a sequel to, sialolithiasis in any of these cases.

The following case* of malignancy developing in the parotid duct in connection with a peculiar calculus-like structure, and terminating fatally, exhibited such unusual features that it is placed on record because of its clinical and pathologic interest.

Case Report.—C. H. (P. G. H. Surg. Path., No. 6670), a white female, aged sixty years, came to the radiologic clinic of the Philadelphia General Hospital, in the service of Dr. John B. Carnett, complaining of pain in the left side of the face. In February, 1925, she had first noticed a small lump behind the lobe of the left ear. Soon after this she experienced periodic attacks of dull, aching pain in the left cheek and which often included the forehead, scalp and ala nasi. These attacks became more frequent, and soon were so severe that she could not sleep. In August, the left side of the face suddenly became swollen, the eyelids drooped, there was much lacrimation, and fluid ran out of the left corner of the mouth when she drank. She stated that for many years there had been a "small lump" inside the left cheek; at about this time this lump began to grow larger "because of irritation caused by her false teeth." Previously, the lump had never been painful, or varied in size. She had never noticed a discharge of any kind from the duct, and the parotid gland had never been swollen or tender. In September 1925, the nodule back of the angle of the left jaw was removed for diagnosis. It proved to be an enlarged cervical lymph node, showing metastatic carcinoma. Dr. E. A. Case, of the Polyclinic Hospital, gave the microscopic diagnosis of "scirrhous carcinoma" (Figs. 6 and 7). Shortly after this the patient came to the Philadelphia General Hospital for relief of pain, and treatment. She had lost 25 pounds in weight during the past eight months.

On physical examination, there was complete left facial paralysis, and the cheek was swollen and puffy. Inside the cheek, in the region of the distal portion of the parotid duct, and about 1 cm. from its mouth, a small, firm, spherical nodule, apparently about 1 cm. in diameter, was felt. This nodule was fixed to the tissues, and was not tender on palpation. Cyst formation or glandular enlargement was not demonstrable. There was no ulceration or induration of the buccal mucosa. A roentgenogram of the nodule revealed a shadow suggestive of calculus or tissue undergoing calcification (Fig. 1). The remaining physical findings were irrelevant. The laboratory examinations were negative, except that the red blood cell count was 3,800,000.

October 8, 1925, under local anesthesia, Dr. Carnett excised a small, apparently encapsulated, whitish, calcific nodule from the distal portion of the parotid duct. The patient was discharged October 21, with the facial condition improved. She was readmitted December 23, because of severe and frequent pains in the left half of the head. Despite numerous applications of radium, she gradually failed and became cachectic. Local

* I am indebted to Dr. John B. Carnett, of Philadelphia, for the use of the clinical data in this case.

recurrence was never demonstrable, but there were clinical evidences of metastasis. Exitus occurred in June, 1926. Necropsy was not permitted.

Pathologic Study. The excised mass consisted of a firm, rounded, calcific structure, surrounded by a tightly fitting capsule. A tag of buccal mucosa was attached. The nodule was sectionable (Fig. 2); the cut surface was grayish-white, and the tumor appeared to be composed of dense fibrohyaline tissue, throughout which were scattered many calcified areas. The attached tissues were infiltrated, and fixed to the nodule; malignancy was not suspected. Grossly the specimen was regarded as an atypical salivary calculus about which an extensive chronic inflammatory reaction had occurred.

Microscopically, an anaplastic or undifferentiated squamous-cell carcinoma was seen growing around, and into, the nodule (Figs. 3 and 4). The nodule itself was composed of very dense fibrohyaline tissue, throughout which many foci of calcification were demonstrable. It did not have the structure of a true calcific salivary concretion. The cancer cells were large and spheroidal in shape; the nuclei were large, vesicular, and deeply stained; the nucleoli were enlarged and prominent. Numerous mitotic figures were seen (Fig. 5). Prickles and pearly bodies were not demonstrable. Small nests and cords of cells invaded the neighboring tissues, and occasionally the nodule proper (Fig. 4) without recognizable structure formation. Histologically these cancer cells resembled modified, immature, squamous epithelial cells.

Sections prepared from the cervical lymph node metastasis (Figs. 6 and 7) revealed a secondary neoplastic growth composed of cells, very similar in appearance to those of the primary tumor.

Dr. James Ewing, of New York, in confirming our diagnosis, stated that he had never seen a carcinoma develop from, or in association with, a calculus in Stensen's duct.

Comment. The possible etiologic relationship of cancer to lithiasis is generally recognized, and, in the light of available data seems fairly definitely established in certain organs. Instances of carcinoma of the biliary tract associated with biliary calculi are well known. Ewing,³ in reviewing the literature on the subject, found that gall stones were present in 69 to 100 per cent of the cases of gall bladder cancer studied, and that the proportion of cases of cholelithiasis which develop cancer is estimated from 4 to 18 per cent. Slade's⁴ study also indicates that the two occur together in a high percentage of cases; he found that the calculi were usually rough when associated with cancer, and concluded that gall stones might be looked upon as a determining cause of gall bladder malignancy.

Carcinoma of the urinary tract associated with urinary calculi is less frequently seen. Coryell⁵ reported 9 cases of concomitant renal cancer and stone, and Menétrier and Martinez⁶ describe in detail a case they have observed in which it was shown that the stone actually prepared the ground for the development of cancer by chronic irritation of the epithelium. We have been unable to find any recorded instances of ureteral or urinary bladder cancer associated with ureteral or vesical calculi. Boyd⁷ states that no relationship has ever been shown to exist between carcinoma of the bladder and stone.

Minet's⁸ case of pancreatic malignancy, occurring with pancreatic lithiasis is unusual and interesting.

Salivary calculi are relatively common, yet infrequent compared to the incidence of biliary and urinary calculi. Edington⁹ reports 9 cases of salivary lithiasis, 8 occurring in the submaxillary duct, and one in the parotid duct. In no instance were the sequelæ and complications other than obstruction, enlargement of the respective gland, and secondary infection. Bailey¹⁰ refers to the 20 cases of cancer of the submaxillary gland on record, and states that "there is very little evidence to show that calculi predispose to this condition."

The relatively high frequency of carcinoma of the gall bladder occurring in association with cholelithiasis, as compared with the rather low incidence of associated urinary tract malignancy and calculi, and the extreme rareness of concomitant salivary duct malignancy and stone may be due to several factors. According to Wells¹¹ the majority of gall stones are composed chiefly of cholesterol, in combination with the calcium salts of bile pigment, and small amounts of organic and inorganic material. The rough, rounded crystalline stones often contain over 90 per cent of cholesterol. Urinary calculi vary considerably in composition, but consist mainly of urates, oxalates, carbonates, and phosphates in combination with calcium, ammonium and magnesium. Pure uric acid and calcium oxalate stones are occasionally met with in acid urine; in the presence of infection, phosphates and urates are deposited. Pancreatic stones consist almost wholly of calcium carbonate; varying amounts of calcium phosphate and magnesium carbonate are occasionally present.

Salivary calculi are rather similar to pancreatic stones, and are composed chiefly of calcium carbonate and phosphate, in combination with traces of organic matter. Pathologic deposition of calcium salts in diseased tissues occurs ordinarily in the ratio of six parts of calcium phosphate to one part of calcium carbonate; traces of magnesium phosphate may be present.

Infection and inflammation sooner or later supervene on lithiasis in the majority of cases. Coincident with this the blood calcium rises, and there follows, as a rule, deposition of calcium salts over concretions which were originally of pure and specific composition.

When these data are analyzed and are balanced against the clinical and pathologic findings as regards tissue changes due to lithiasis, it appears that cholesterol is the only constituent of calculi that possesses possible carcinogenic properties. Excepting certain apparently harmless elements found mainly in urinary stones, the remaining ordinary components of calculi are common to practically all calculi, and pathologic processes where calcification occurs. Roffo¹² has found a high percentage of cholesterol in early and well-developed cancerous lesions, with associated hypercholesterolemia

He concludes that cholesterol is involved with the enhanced nutritional function of tissue growth as known in neoplasia, and that it may act as a precursory agent in the development of malignant disease. The cholesterol metabolism in malignancy, and its specific effect on tissue proliferation remain subjects for further investigation, but from the striking relationship that exists between gall stones and gall bladder cancer, the possibility of cholesterol playing an important, and perhaps etiologic, rôle in the development and behavior of certain types of cancer is strongly suggested.

The constant irritation of the epithelial cells of the mucosa by calculi, particularly in the presence of infection, is an illustration *par excellence* of the view commonly held that chronic irritation is a prominent factor in inducing malignant transformation of the epithelium. Yet, on analysis, one is struck by the relative rareness of associated stone and cancer in all organs except the gall bladder. The gall bladder is lined by tall, columnar, mucus-secreting cells; in practically every other organ which is the seat of calculi, the lining mucosa is of the squamous-cell or transitional-cell type. This might suggest that glandular mucosa is more susceptible to malignant transformation than squamous mucosa under the influence of chronic irritation, but until the effect of cholesterol is determined such a conclusion is not justifiable. Infection, inflammation, and irritation bring about changes in the mucosa which in time are recognized as hypertrophy, and occasionally, metaplasia of the epithelium, with attendant surrounding fibrosis. That a process which is essentially protective and defensive in its reaction to harmful agents should, through overstimulation, become self-destructive, seems unnatural, yet there is evidence that, following metaplasia of epithelium, there ensues an actual malignant transformation of the changed cells in rare cases. We believe our case to be an example of this.

There are certain peculiarities about our case. The nodule, although largely calcified, cannot be regarded as a true calcific salivary concretion because of its histologic appearance. Basically it appears to have been a fibrous structure that in time became hyalinized and partly calcified. Its location and long period of duration probably caused it to act very much like a sialolith, however, causing partial obstruction. One is tempted to explain matters on the supposition that the structure, whatever its true nature, over a long period of time brought about, possibly through mild continuous irritative activity, a change or metaplasia in the short columnar cells that normally line the parotid duct, which, in turn, eventuated into malignant transformation of these cells. This conception fits both the histologic picture and the clinical course of the case. The cancer cells were anaplastic and appeared to be growing rapidly, microscopically. Clinically metastasis occurred relatively early and a fatal termination came soon. In addition to its clinical and pathologic interest, the case is worthy of record in that it designates the parotid duct as a rare source of carcinoma of the cheek.

Summary. 1. An instance of carcinoma developing in the parotid duct in association with a peculiar, calculus-like structure, is recorded.

2. The etiologic relationship of lithiasis to malignancy is reviewed. Associated stone and cancer are well known in the biliary tract. In all other organs where calculi occur, carcinoma seldom supervenes on lithiasis. In the salivary system, associated stone and cancer are practically unknown.

3. It is suggested that cholesterol plays an important rôle in the development of gall bladder cancer. Chronic irritation, secondary infection, and inflammation bring about hypertrophic and proliferative changes in the mucosal epithelium, but do not appear to be carcinogenic *per se*. Several factors appear to be operative in inducing the malignant transformation of epithelium in the presence of calculi.

4. Metaplasia of epithelium occurs rarely as an atypical reaction to long-continued irritation. Malignant transformation of the changed epithelium may follow this.

5. Our case designates the parotid duct as a rare source of carcinoma of the cheek.

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THE MEDICAL TREATMENT OF ULCER OF THE STOMACH.*

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THE treatment of gastric ulcer is a less congenial subject to the physician than the treatment of duodenal ulcer, because the former

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is usually a more serious condition and the results of medical treatment less striking. In fact, we occasionally meet the opinion that there is no medical treatment of gastric ulcer; that the patient should go at once to a surgeon when this diagnosis is made. With this, our own experience does not agree. We will give our observations in a series of 51 cases in private practice in which this diagnosis has been made, and which have been followed for five years or more, giving the details of the medical treatment used and the end results which have been obtained.

The Accuracy of Modern Diagnosis. Accurate diagnosis is essential to good treatment. In the past the surgeon had a great advantage over the physician; usually he knew when he was treating gastric ulcer, because he had seen and felt it, and the physician had not. Many ulcers were overlooked by the physician and called "hyperacidity," and many so-called ulcers were given medical treatment, and included in medical statistics which were not ulcers at all, but neuroses, pathologic gall bladders, or appendices; in addition it was often not possible to make a definite distinction between gastric and duodenal ulcers. This led to a sharp contrast between medical and surgical statistics.

Our present-day accuracy of diagnosis of gastric ulcer without operation is over 90 per cent. It is rare in a carefully studied case either to overlook an ulcer, or to diagnose ulcer when it is not present. This is largely due to the addition of the Roentgen ray to our other methods. The Roentgen ray not only discovers the deformity of ulcer, but locates it in the stomach or duodenum, gives us an idea of the size of lesser curvature ulcers, and by the Graham test and in other ways detects many pathologic gall bladders simulating ulcer. It may also discover chronic changes in the appendix. On this basis, a new set of medical ulcer statistics have been accumulating in the last ten years, which have real value.

Some difficulties in diagnosis still are met. The cases with gastric hemorrhage with few or no digestive symptoms and negative Roentgen ray findings are hard to classify. An occasional pyloric cancer is hard to distinguish from pyloric ulcer at the first examination, but is almost always discovered when followed with painstaking care for a short time.

The accuracy of modern diagnosis brings with it the responsibility for earlier and better treatment. The long medical histories with years of medical treatment are a reproach. Many ulcers in private practice have gone unrecognized for years because they were not taken seriously enough, and no Roentgen ray examination made. It is safe to say that fully one-half the gastric ulcers have been diagnosed late.

It is important for the present-day practitioner to have the *early* ulcer picture in mind, the common hunger pain or "hyperacidity" syndrome, the relief by food and by alkalies, and the

Roentgen ray deformity, and not to think of severe pain, hemorrhage, anemia, obstruction and perforation as the cardinal symptoms.

By using the Roentgen ray promptly we can often make an earlier diagnosis when the patient is younger, when remissions are long and there are no complications. This has an important effect on treatment. We are not asking impossibilities; early cancer diagnosis is very hard; early ulcer diagnosis is not.

The Selection of Cases for Medical Treatment. We think first of the absence of complications, such as bleeding, obstruction, and, of course, perforation. We will take up later the limits of medical treatment in bleeding and obstructive cases. Gastric ulcers are less favorable than duodenal, not so much on account of the cancer risk, but because they do not give as good results under medical treatment. We must also give medical treatment to many patients because they prefer it if it can be made successful, and to some others because of lesions outside the digestive tract which make operation dangerous.

In selecting patients for medical treatment I wish to especially emphasize that the younger ones do better. We get a decidedly higher percentage of cures in patients under forty-five years than over. The most favorable cases are those which have short histories, short attacks and long remissions (the so-called acute recurrent type of ulcer) and those who are intelligent and are willing to see the doctor occasionally during a period of several years, even when symptom-free. We can make medical treatment a success with a larger proportion of private than hospital patients, because of their greater intelligence, easier circumstances, better food and better contact with the physician.

We used to think that the discovery of an hour-glass stomach was an indication for operation. We now realize that this is true only when it causes symptoms. We have several cases who have been under occasional observation for years, who have no obstruction, and enjoy excellent health, and would not consider an operation. Dr. F. H. Lahey, of Boston, has reported the same experience.

The General Treatment. The plan of medical treatment must be simple, logical and above all practicable. Most people cannot afford to "make a pet" of an ulcer, as Dr. Mayo says, or to devote much time and money to repeated hospital treatment.

We like to classify and plan separately for gastric and for duodenal ulcer. The treatment is very similar, but the medical responsibility, the follow-up, the results and the surgical aspects differ somewhat.

Our treatment is still largely symptomatic, since the cause is not definitely known, but evidently the mixed result of chemical, mechanical, infectious and nervous factors. Vague talk about diatheses gives no practical help at present. We will sum up briefly

the chief factors in medical treatment in the approximate order of importance.

A *bland diet* is essential and easily understood. The Leube and Lenhartz and Sippy diet use much the same foods. We need ride no hobbies, but consult the taste of our patient. Milk and egg, milk and cream or cereal gruels at the start do equally well.

Frequent feeding is the great thing, and must be emphasized, six times a day or even more at the beginning. This is easily arranged with ambulatory cases by means of a thermos bottle. We have given up the use of duodenal feeding in ulcer as it is less comfortable for the patient and has no real advantages over mouth feeding.

These are the two routine diets which we use, which allow sufficient choice of food to suit individual tastes. The "periods" in Diet I are approximately a week, but are varied to suit the severity of the case. The strict Lenhartz régime of egg and milk, only in the first week is distasteful to some people. We prefer to vary it with gruels and milk and cream.

Diet I. *First Period.* Strained cereal gruels or strained cream soups made from vegetables (such as potato, celery, corn, asparagus) or milk and cream; equal parts are given in one- or two-hourly feedings, beginning with 1 ounce and increasing up to 3 or 4 ounces. If desired, the Lenhartz feeding may be given, namely, 8 ounces of milk and 2 eggs beaten up and divided into twelve feedings, one every hour. Each day add 1 more egg and 3 ounces of milk until 6 eggs and 1 quart of milk are taken. On the third day add $\frac{1}{2}$ ounce of sugar or milk sugar to the beaten eggs, gradually increasing to 1 ounce of sugar.

Second Period. Two or 3 eggs, soft cooked; three feedings of 1 ounce each of boiled rice, or other well-cooked cereal (not oatmeal) served with sugar and cream. One-half to 1 ounce of butter per day. Gruels, cream soups, milk, egg and milk, 1 or 2 pieces of very dry toast, well chewed, or milk toast, plain crackers, macaroni, Mellen's Food, or malted milk, junket, custard, cream toast, ice cream. Six meals a day.

Third Period. Add 1 or 2 ounces of tender beef, chicken, chop or steak, daily; also simple cornstarch, custard and rice puddings.

Fourth Period. Add well-cooked mashed potato or squash, vegetable purées, finely chopped spinach; apple sauce or stewed pear.

General Directions. Eat slowly, chew well; no very hot or very cold foods; no worry at meals. Never eat until overfilled. Take a little lunch between meals, for example, a glass of milk, malted milk or cocoa, with 1 or 2 crackers. No raw fruit or vegetables for six months.

Diet II. The general plan of the diet is three moderate-sized meals at regular intervals in the day, and supplemental meals of malted milk or milk reinforced with cream, cocoa and crackers between meals and before retiring. All of the solid foods should be tender,

cut very fine on the plate and thoroughly masticated before swallowing. Altogether, foods should be taken at least five or six times a day in one or the other of the two types of meals. No meat broths, condiments, spices, coffee, "soda water," alcohol, coarse or salted food, very hot or very cold foods.

The foods permitted for the main meals are as follows: Cream soups, eggs, soft cooked (2 to 4 in a day), cereals (well-cooked) with cream in the morning, rice, macaroni, well-cooked and mashed potato or squash, vegetable purées, finely chopped spinach (no green vegetables, raw fruits, berries or nuts). Desserts, any made of milk, eggs and cereals (custards, simple puddings) and jellies, cream cheese, cooked fruit—apple, pear, peach, prunes. The best drink at the meals is water, hot cocoa, or malted milk. Butter, cream, milk, eggs, cereals and bread remain the main foods of the diet. *Olive oil may be taken after the main meals, a dessertspoonful or tablespoonful.*

After the first or second week fresh beef, lamb or chicken, roasted or broiled, or fresh fish, broiled, baked or boiled, may be taken once a day (no mackerel or salmon).

Rest is important. In most cases of gastric ulcer a week or two in bed at the beginning of the treatment is desirable. Some need twice this time, and some milder cases give good results with ambulatory treatment (a large percentage of our duodenal cases do well on ambulatory treatment). It is usually easier to arrange diagnostic tests and to begin systematic treatment in a hospital rather than at home.

Drugs. We do not use many; even alkalies are not essential and can be omitted in many bed cases with good results. They are very useful; however, they simplify treatment, especially at first. We use them regularly in the form of the familiar Sippy powders (No. 1.—Sodii bicarb., magnesii oxid. pond. āā, 5j; No. 2.—Sodii bicarb, 5iij and calcii carbonat., 5j), given alternately in 20 to 30 gr. doses midway between feedings, beginning with four to six times a day and usually dropping to two or three times a day in a week or two. No. 1 powder may have to be reduced or replaced by No. 2 if it is too laxative. Magnesium oxide is used in amount large enough to give one daily formed stool, the rest of the alkali being given as sodium bicarbonate and calcium carbonate. The use of two or three powders a day midway between feedings is best continued for several months, after that we often omit the routine use of powders and depend chiefly on the diet and hygienic measures, using the alkalies only occasionally. Some patients take one to three powders a day, for six to twelve months.

An excess of alkali may cause gastric irritation or even an actual toxemia with renal changes which has been described by Hardt and Rivers, and is characterized by dizziness, headache, nausea and vomiting and important changes in the blood chemistry. They

found it in 30 per cent of a series of thirty ulcers on the Sippy treatment. It cleared up in one or two days on stopping the alkalies. They consider that alkaline therapy directed to complete neutralization of gastric acidity may be harmful. Dr. S. M. Jordon, of the Lahey Clinic, of Boston, found alkalosis in only 3 per cent of a series of 100 carefully studied cases of ulcer on the Sippy régime. We have found gastric irritation very rare with our moderate use of alkalies, and actual alkalosis even more rare. We have seen it in only a small fraction of the cases with pyloric obstruction, and will take it up more fully under that heading.

The "hunger pain" of ulcer is the result of many factors, such as food irritation, hyperacidity, pyloric spasm, hyperperistalsis, hunger contractions and hyperesthesia. Alkalies are especially useful when the pain is accompanied by gastric distention, as in addition to neutralizing acid; they help partly by causing belching of gas and by relaxing the pylorus.

Atropin is useful to relax spasm, quiet peristalsis and check true hypersecretion. Rather large doses are usually needed $\frac{1}{100}$ to $\frac{1}{50}$ gr. ($\frac{1}{2}$ to 1 mg.) of atropin sulphate, given by mouth, once or twice a day. It helps to carry the patient through the night, which is much the longest interval between feedings, and avoid "night pain" at 1 to 3 A.M.

Bismuth salts have a remarkable quality of covering a large surface of mucous membrane and have some value as a protective in ulcer, but we do not use them much because the diet in the early weeks is very bland and apt to be constipating.

Tobacco is important and unfortunately often allowed. Many proved cases of ulcer come to me smoking ten to twenty cigarettes or four or five cigars a day. It has an important effect in stimulating spasm and gastric secretion; it antagonizes the rest of the treatment and should be cut very low or omitted for some months at least.

It is important to remove infection in the remission period, such as septic teeth, tonsils, sinuses, and so forth. If the appendix or gall bladder are involved this puts the patient in the major surgical group.

Treatment in Remissions. This is a crucial point in medical treatment which is often neglected. Relief of pain is not a cure. It is usually easy to stop a recurrent attack in ulcer, to relieve pain, check vomiting and make the patient comfortable within a short time, usually in a few days. Our difficulties begin when the patient is symptom free. At first he is anxious, perhaps frightened, when the diagnosis of ulcer is made, and is very willing to coöperate; later the fear of the disease wears off when he finds himself promptly relieved and feeling entirely well. Both patient and doctor may get too lax, the diet is increased too rapidly, tobacco may be abused, the patient is too active physically, he gets tired, a little infection

may appear in the fall or spring and we have a recurrence of the ulcer.

This sort of thing is the bane of medical treatment, which should be well ordered and progressive, like that of diabetes. A foolish diabetic does not keep well, neither does a foolish ulcer patient; we may go a step further and say to the doctor, that an ulcer which is foolishly treated does not get well. The symptom-free ulcer patient is like the sugar-free diabetic—he is in a happy condition, which must be continued even at some sacrifice. The treatment is not really irksome, the restrictions are mild compared to those in diabetes, but they must be followed to get a permanent cure.

Almost any doctor can stop an attack; it is what we do in remissions which count the most—in educating the patient, in rooting out infections and preventing recurrence. We ought to explain to the patient at the start the importance and chronic nature of the disease, the tendency to recurrence and the duration of some supervision for at least two years. Much medical treatment still lacks a logical plan and is not systematic and thorough enough to get good results. If we recognize our shortcomings we can soon end them.

Follow-up System. A good follow-up system is vital in ulcer, just as in diabetes. We need occasional office reports, occasional examination of the stool for blood, occasional later examinations of the stomach with the Roentgen ray. It is never fair to let the patient shift for himself and try his luck on the wrong food.

A late follow-up of these patients for three to five years or more is also of great value in getting real end results of treatment, which are often neglected. I am suspicious of some of the medical statistics of "cures" in ulcer and feel like asking how long the cases have been followed up. The figures for so-called "cures" are distinctly higher in the first year or two after treatment is begun, than in three to five years or more; often 10 or 15 per cent must be taken off the early high figures of the patients who are well.

Use of Roentgen Ray and Occult Blood Tests to Follow the Results of Medical Treatment. In judging the results of medical treatment, we depend largely on changes in the patient's symptoms and signs (disappearance of hunger pain and distress, vomiting, gross bleeding, weight changes, tenderness and so forth), but in many cases we may get valuable help from blood tests and from the Roentgen ray.

Testing the feces for blood is an important routine. A meat-free diet must be used, and low intestinal bleeding excluded. Meat is not usually added to the routine ulcer diet until the third or fourth week, so there is no interference with early blood tests of the stools. Positive occult blood tests showing an active ulcer or recent hemorrhage usually entirely disappear in five to seven days under medical treatment. Any delay in the disappearance of blood is important and must be explained. It may be due to an ulcer which is not controlled by medical treatment and continues to bleed, or to a

cancerous ulceration; in both cases surgery must be considered promptly.

The Roentgen ray not only gives us the size and position of the ulcer, but enables us in a large degree to follow the course of healing. It is important to know just what a gastric ulcer is doing under medical treatment. We find that the peristalsis becomes less active and more normal, pyloric spasm lessens, the stomach empties better and above all the local deformity of the ulcer disappears, the crater fills up and the edges smooth out often in from one to four weeks. This is best seen in a lesser curvature ulcer, where we have it in profile (Figs. 1 to 6). In pyloric ulcer some local deformity due to spasm or scar tissue is often very persistent.

It is needless to say that these changes must be carefully correlated with changes in symptoms and other physical signs. Occasionally the Roentgen ray signs may be more important than the clinical. The patient may lose his symptoms and gain weight, but lack of healing shown by the Roentgen ray may give the best indication of a severe lesion. The best time for this reëxamination of the stomach is at the end of one or two weeks after treatment had been begun, again after one or two months, and at some later period.

There is some objection to Roentgen ray studies of local deformity as an index of the healing of an ulcer. The crater may fill with food or mucus and appear healed, or the stomach be rotated a little at subsequent examinations and the ulcer hidden. These objections call for careful work and interpretation, but are not serious. This Roentgen ray evidence of the rapid healing of gastric ulcer has been checked up by operation in several of our cases and found to be an actual fact.

This Roentgen ray study, together with the examination of resected material, has taught us much of the life history of ulcer—the time taken to form and heal at different stages and the degree of healing in intermissions. The discovery, that good-sized lesser curvature ulcers will disappear almost completely within four to six weeks, has been a surprise.

Late Results of Medical Treatment in Private Practice. The material is as follows: Of 51 gastric ulcers, 9 were operated upon at once and 41 put on medical treatment and tabulated below; 135 duodenal ulcers who were put on medical treatment are listed for comparison. These patients have been thoroughly studied by modern methods, and we have every reason to believe that 90 to 95 per cent at least were actual ulcers. They have been followed for three to five years or more to get actual late results. This is essential in this chronic disease when remissions and recurrences are so characteristic. Doubtful cases and short follow-ups have been excluded.

TABLE I. RESULTS OF MEDICAL TREATMENT.

	Gastric ulcer, 41 cases, per cent.	Duodenal ulcer, 135 cases, per cent.
Well	39.0	59.2
Better	29.0	22.2
No better	2.5	4.5
Later operation, after medical treatment	24.5	14.1
Died under medical treatment	5.0	0

You will note that more than one-third of the gastric ulcers are well, less than one-third better and about one-fourth were operated upon after unsuccessful medical treatment. Among the well cases the duodenal ulcers easily lead.

If our per cent of well cases under medical treatment, 39 per cent gastric ulcer and 59.2 per cent duodenal, seems moderate in comparison with some other medical figures, remember that the patients have been followed for three to five years, and that figures showing apparent cure will be 10 to 15 per cent higher at the end of only six months or a year, because some of these cases recur later. If these figures seem high to some surgeons, remember that the cases include many of the earlier, milder type of ulcer, and that painstaking care has been taken in the medical treatment in periods of remission, in educating the patient as in diabetes. Some cases listed as better, but not well, would no doubt be better still with an operation, but the patient often refuses if he is almost well or the intermissions are long. Nearly twice as many gastric as duodenal ulcers were operated upon after unsuccessful medical treatment.

There were no deaths among our duodenal ulcers under medical treatment. The 2 cases (5 per cent) of gastric ulcer died, 1 of cancer, apparently developing in a large inoperable ulcer in an elderly man with a bad heart, and 1 of a complicating diverticulitis of the sigmoid.

In looking over ulcer statistics we must always note what group is studied, whether a selected severe group sent to a great surgical clinic, or an average or milder group sent to a medical man in hope of medical relief. Our medical statistics give a general impression, but not mathematical accuracy, because patients occasionally change from one group to another, and while averages are interesting, the prognosis of the individual case may be different, either above or below the average.

The Advantages, Limitations and Risks of Medical Treatment. The advantages of medical treatment are that most patients prefer it. There is no mortality from the treatment itself, and nearly 40 per cent of gastric ulcers, and nearly 60 per cent of duodenal ulcers, get well and stay well, even if followed for a long period.

The disadvantages are that it is more tedious, requires more self

control (like diabetes), and an unintelligent or poor patient may find it difficult to carry out, and allied pathology in the abdomen may not be discovered and removed at the start.

There is some overlapping of medical and surgical treatment. There are cases which are best treated medically, and others best treated surgically, but there are some which may be treated in either way. The treatment sometimes depends on the clinic to which the patient goes. The patient with moderate grade-spastic pyloric obstruction going to Sippy's Clinic some years ago would have undoubtedly had medical treatment, the same patient going to a surgical clinic would undoubtedly have had a gastroenterostomy.

It is unwise to have medical and surgical treatment overlap too much. It is unwise for the physician to keep cases of pyloric obstruction too long on medical treatment in the hope that pyloric spasm will entirely disappear. It is unwise for the young surgeon to operate upon many uncomplicated duodenal ulcers in young persons with long remissions, who could easily be cured by medical means. The patient has a right to expect the kind of prompt and efficient treatment which is simplest and will suit him best. The doctor does not always make the decision. There are illogic reactions to operation on the patient's part. We have the recurrent bleeding or very obstructing ulcer who refuses operation, and the young neurotic uncomplicated case who "would like to try a gastroenterostomy."

The Ulcer-cancer Question. The possible development of cancer on the base or border of a chronic gastric ulcer has an important bearing on the treatment, and is a difficult subject to discuss because there has been so little agreement among pathologists about it. We will quote only a few typical figures which vary from 71 per cent (McCarthy), 21 per cent (Finsterer) to 5 per cent (Ewing), with many other pathologists near the lower figures (Aschoff, rare; Crile, probably less than 5 per cent; and so forth).

Each man is impressed by his own experience and that in his own locality. Ours all points one way. In our series there was only 1 case in 51 gastric ulcers, about 2 per cent. At the Peter Bent Brigham Hospital, in Boston, they record 4.5 per cent in 201 cases. At the Massachusetts General Hospital Dr. Wright, the pathologist, says: "Cancer developing on chronic ulcer of the stomach is very rare, that is, cancer found in only one portion of a chronic ulcer. I have seen only a few, perhaps 3 or 4 cases, in my life."

Dr. F. B. Mallory, the pathologist at the Boston City Hospital, says: "We have ulcerating cancers, but I have never seen a cancer originating in peptic ulcer, that is, a chronic ulcer with cancer nests in the border or base."

A number of excellent clinicians who have treated many cases of ulcer of the stomach are not sure that a single case treated in their

clinics has later developed cancer, and others a possible 1 to 5 per cent. Einhorn, Rehfuess, Smithies, Soper, Friedenwald, Alvarez, Richard Cabot and Harlow Brooks place the figure variously at 0 to 1 or 2 or 5 per cent. These reports of cases having prolonged medical treatment would be just the ones to show cancer development if such a change occurred. If there were 70 per cent of cancers lurking in the background we should be swamped with them.

The willingness of the surgeon to do a gastroenterostomy in gastric ulcer throws light on his opinion of the importance and frequency of cancer development. Gastroenterostomy with its lower mortality was the operation done in nearly one-half our gastric ulcer series without later development of a single cancer as far as we know.

One is left with the impression that nearly all cancers supposed to develop from chronic ulcer have been malignant from the start.

There is no doubt that a large number of gastric ulcers are best treated surgically. In our series of 51 cases 9 were operated upon at once and 10 more were operated upon later after medical treatment, making 37.2 per cent in all. There is also no doubt that a considerable number, 39 per cent in our medical series, get a satisfactory result from medical treatment without taking undue risk. It certainly is not necessary to treat gastric ulcers with the idea that a large number will turn to cancer, for if this is done the cases lost at operation might easily be greater than the cases lost by cancer.

We started our medical treatment of gastric ulcer with a healthy fear of the possibilities of cancer, but were encouraged by the present opportunities to see what is happening to the ulcer by means of the Roentgen ray and by the rapid disappearance of many gastric ulcers under medical treatment in four to six weeks, and by finding that cancer developing on our gastric ulcers was a rarity (approximately 2 per cent). Our only case was a very large lesser curvature ulcer in an elderly physician with a bad heart, which was recognized at once as a dangerous ulcer on account of its size, but was considered inoperable by both patient and surgeon, and was not controlled by medical treatment. This case was not proved pathologically, but the clinical evidence of a cancer developing on a gastric ulcer seemed reasonably clear.

We began our medical treatment of gastric ulcer with private patients where the surgeon hesitates, such as young persons, old ladies, high lesser curvature cases and gradually extended it to some others, especially small lesser curvature ulcers.

Any physician who attempts medical treatment of gastric ulcer must do it with his eyes open and with a due sense of responsibility and a willingness to follow his cases with painstaking care by means of Roentgen ray examination, blood tests, tests of the empty-

ing of the stomach and so forth. If this is done, medical treatment is reasonable and safe, favorable cases are continued on medical treatment and unfavorable ones are promptly weeded out and referred to a surgeon. We have had no serious mistakes under this scheme, no serious complications, no unexpected cancer developing on our ulcers under continued medical treatment.

The life history of gastric ulcer under medical treatment is very interesting. We often see a rapid disappearance of the ulcer deformity in one or two months. This is readily shown by the Roentgen ray in lesser curvature ulcers, and has been verified by operation, where this has been occasionally done after a few weeks of medical treatment. In gross appearance we might even compare the active ulcer to a boil with much irritation and infection, with much round-cell infiltration and swelling. In a month or two we find the swelling all gone, the crater filled up, the ulcer flat and little but scar tissue left (Figs. 1 to 6).

Treatment of Hemorrhage and Obstruction. **HEMORRHAGE.** We all agree that medical treatment of the first gross hemorrhage in ulcer is much the safest and best. Nine cases out of 10 recover from acute hemorrhage, even if large. We all agree that patients who have recurrent hemorrhages under careful medical treatment need surgery, preferably excision. Transfusion of blood has made the operation in such cases far safer than in the past.

An occasional serious dilemma is probably unavoidable even with early surgical consultation. Operation may be delayed in the hope of getting the patient in better condition and another hemorrhage may cause death before or after the operation is done.

The details of medical treatment are the old-fashioned ones, absolute rest, opium, low liquids, low stimulation, rectal feeding for a day or two with the important addition of transfusion of blood. We do not use coagulants, such as rabbit serum, preparations of fibrin ferment or platelets, because these coagulants are not only abundant in the blood after acute hemorrhage, but usually increased in amount. Small doses of adrenalin by mouth are too much diluted before they reach the stomach to have much local effect.

PYLORIC OBSTRUCTION. This is due in one-tenth of the cases to organic tissue narrowing, in nine-tenths to spasm (W. J. Mayo). Such cases are especially important and deserve careful hospital management. We judge the case in regard to medical treatment by the amount of gastric residue at the start and by the response to treatment. Those with residues of 50 per cent or more, six hours after a barium meal, and those with considerable food residues, twelve hours after a motor meal, are usually surgical, and cases with twenty-four-hour barium residue are practically always surgical. Unless six-hour residues disappear in a few weeks, surgical treatment is usually best; we owe it to our patients to get them

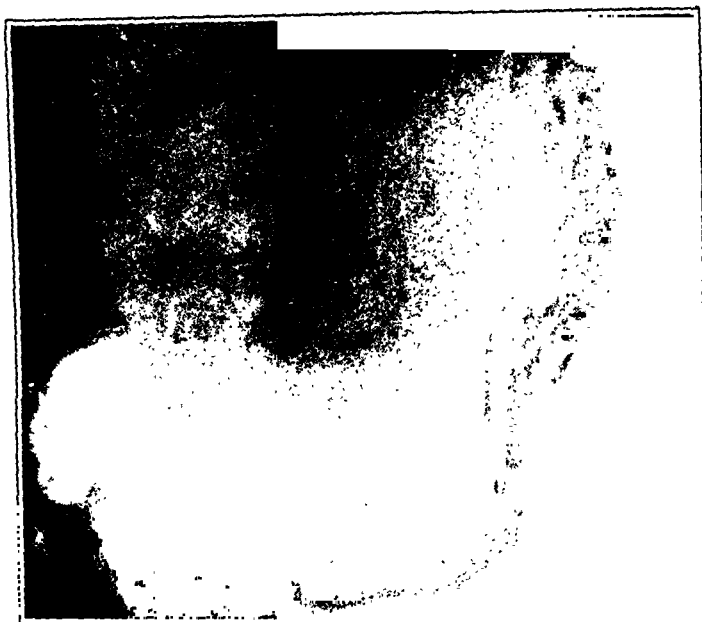


FIG. 1.—(Case I.) Medium-sized gastric ulcer on the lesser curvature at the beginning of medical treatment.

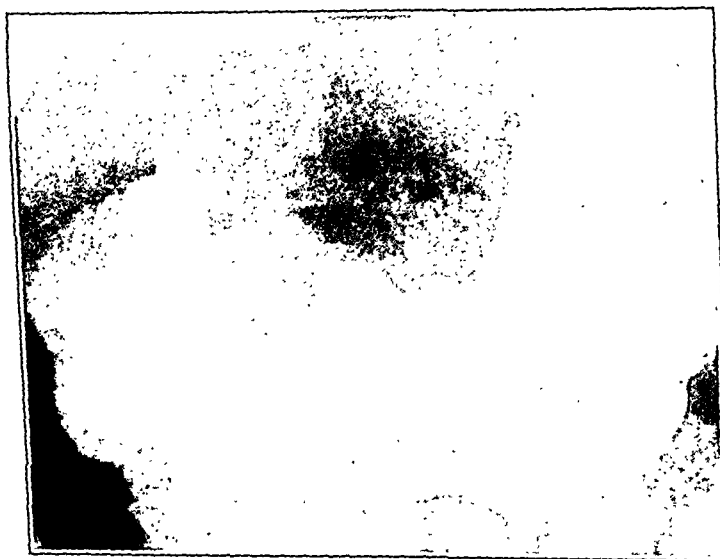


FIG. 2.—(Case I.) Five days later: Slight change; ulcer a little flatter, crater less deep.



FIG. 3.—(Case I.) One month later: Marked change; ulcer deformity almost gone, a trace of the crater remains.



FIG. 4.—(Case I.) Six months later: Ulcer deformity entirely gone; patient well for five months (has continued well for three years).

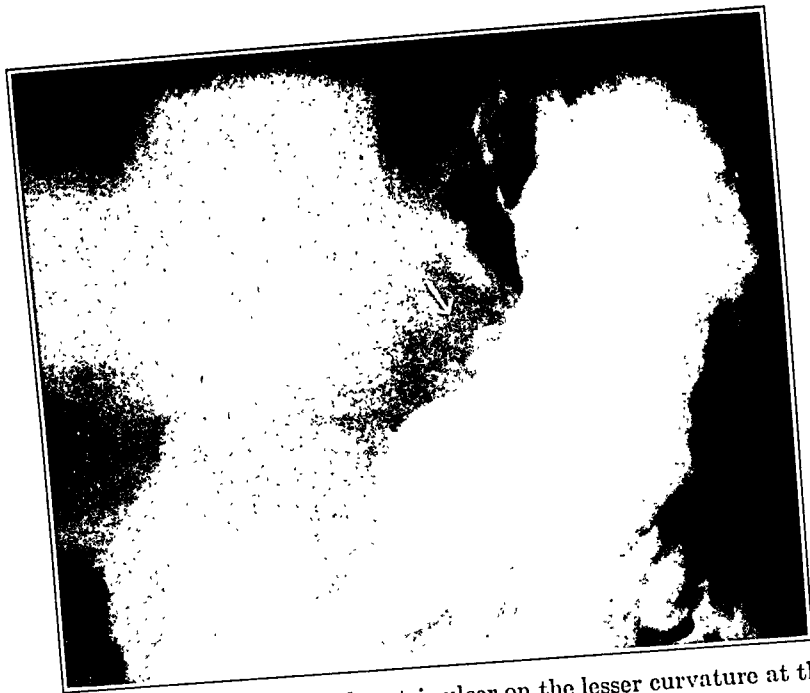


FIG. 5.—(Case II.) Medium-sized gastric ulcer on the lesser curvature at the beginning of medical treatment.

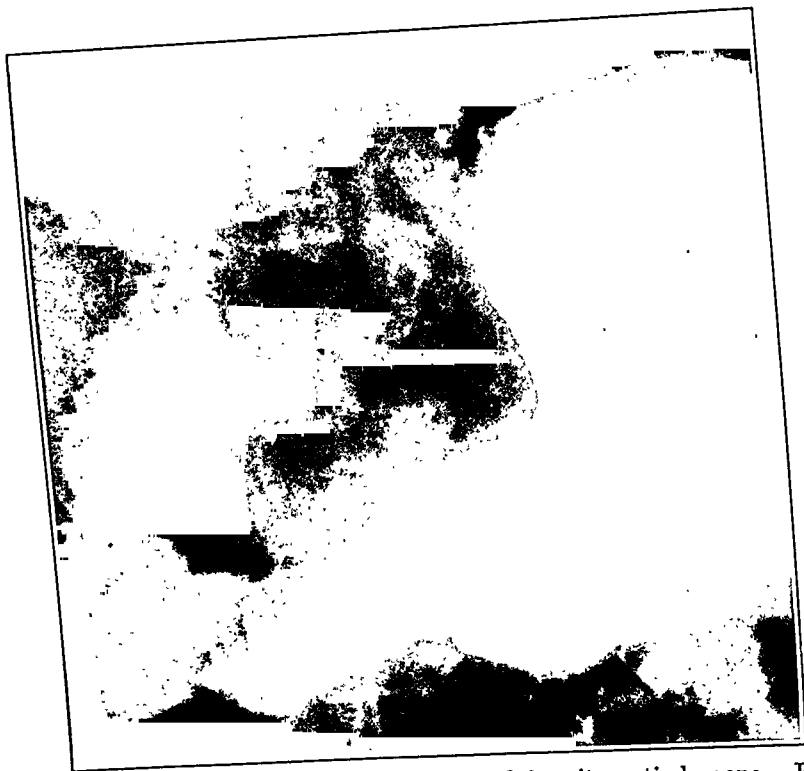


FIG. 6.—(Case II.) One week later: Ulcer deformity entirely gone. Patient is symptom free. (Seven other plates of the stomach taken at this time, at all angles, showed no deformity.)

well in the easiest and safest way, and not to carry medical treatment too far.

We do not use evening or night intubation to remove food residues or excessive acid secretion, as suggested by Sippy. If pyloric spasm does not relax on a bland diet, frequent feedings, rest in bed, alkalies and atropin without intubation, and the stomach does not empty itself normally in two to three weeks, then we usually advise gastroenterostomy, because the chances of recurrence under further medical treatment are large.

There are some patients, however, whose recovery from obstruction is slower, but still satisfactory. They have few symptoms, and may refuse operation and leave the hospital with 30 or 40 per cent six-hour residues after a barium meal. Such patients are always a source of anxiety, but quite often the spastic obstruction slowly, but completely, disappears within one or two months, and the patients remain entirely well for long periods.

There is a definite toxemia in some high-grade cases of pyloric obstruction, which is very serious and important, but fortunately rather rare. We have had little experience with it, having discovered only 2 cases in the last three years, in spite of careful chemical studies in all our cases of pyloric obstruction. This toxemia has been carefully studied by Berkman, Brown, Eusterman, Hartman and Rowntree and by McVicar, of the Mayo Clinic.

The clinical picture is characterized by vomiting, dehydration, shocklike features (prostration, low delirium, low blood pressure, red facies, high hemoglobin), uremia and often by tetany. There is a serious toxic nephritis with a lessened output of the urine, which contains albumin and casts, a low phenolsulphonephthalein excretion and important changes in the blood chemistry, such as high-blood urea nitrogen, low-blood chlorids and an invariable tendency toward alkalosis. Study of the blood chemistry is a more accurate way of measuring severity than the clinical appearance, and enables us to recognize the condition early and watch the progress of treatment.

In treatment, water is indicated to combat dehydration, to counteract shock, to promote diuresis and wash out nitrogenous waste products. Liberal doses of sodium chlorid are given, and sugar has been used to spare the protein. Sodium chlorid, 10 gm., glucose, 100 gm., and water, 1000 cc., are given intravenously or by rectum, once, twice or three times a day, and sodium chlorid solution is given subcutaneously and by mouth. Frequent lavage is used to clean and empty the stomach. Since all cases show a tendency to alkalosis, the use of alkalies is contraindicated. This has proved a very valuable preoperative medical treatment in cases of serious pyloric obstruction, and has greatly reduced the mortality at operation (from 16.5 to 0.6 per cent) at the Mayo Clinic in this limited group.

The presence of alkalosis and toxemia in these serious cases of pyloric obstruction is not, however, a logical argument against the reasonable use of alkalies in the average case of gastric ulcer.

One way to improve our results in ulcer is by earlier diagnosis. These long histories of five to ten years' duration are a reproach. We should give our patients earlier and better treatment; if medical will not do, then surgical. Better medical treatment does not mean a new diet or new drugs, but insistence on frequent feedings, better care in remissions, better education of the patient and a better follow-up system.

Many gastric ulcers are best treated surgically. In our whole series of 51 patients, 9 were operated upon at once and 10 more were operated upon later after medical treatment, making 37.2 per cent in all. We also feel sure that many gastric ulcers get a good lasting result with medical treatment without taking undue risk. In our series of 41 patients on medical treatment 40 per cent consider themselves well at the end of three to five years or more, and 29 per cent more are so much better that they have been unwilling to undergo operation.

It is not necessary to treat gastric ulcer with the idea that large numbers will become cancerous. We have only 1 case in the total series of 51 patients, including those operated upon at once and also those put upon medical treatment who have been followed for from three to five years or more.

A combined medical and surgical routine is the only logical one, medical for the large group of younger, milder uncomplicated cases; surgical for the chronic, serious resistant cases. The value of surgery is not in treating the whole group, but in curing so many difficult cases.

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CHRONIC DUODENAL ILEUS.*

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DURING the past six years considerable interest and not a little controversy have been aroused over the significance of the dilated duodenum and the question as to whether in the condition designated "chronic duodenal ileus" we have a true pathologic and clinical entity. We are all familiar with the importance of the duodenal segment of the gut, with the toxicity of its content when obstructed, and the grave and often fatal constitutional disturbances which follow a complete blockage of its lumen. In cases of so-called gastromesenteric ileus we have both clinical and post-mortem evidence that an organic obstruction of the third part of the duodenum by the root of the mesentery is the active factor in producing the ileus. Thus the emptying of the stomach and the elevation of the pelvis in the prone or lateral position will immediately relieve the condition, and, in fatal cases, the postmortem examination will reveal the stomach and the duodenum, up to the mesenteric root, greatly distended while the bowel beyond is collapsed and empty.

That other forms of acute dilatation of the stomach and the upper reaches of the bowel occur is more than probable, and is no argument against the existence of the one with which we deal here. The rotation of the colon in fetal life, which brings the superior mesenteric vessels to lie athwart the duodenum, is subject to great variation. Imperfect rotation and fixation of the colon are found most frequently in subjects of the asthenic and visceroptotic type and, consequently, it is in this class of individual that duodenal ileus is most commonly met with. The small intestine, with its fluid content, is tolerant of handicaps to the onward passage of its chyme up to the point of complete obstruction, when it manifests its disability in no uncertain fashion. Thus we find a moderate duodenal obstruction persisting for years without symptoms sufficiently dramatic to incriminate the lesion until, finally, a complete obstruction supervenes with symptoms too obvious to be mistaken.

Pathologic Anatomy. Any abnormality of the mesentery will be liable to cause duodenal compression. Thus, the most marked case of duodenal ileus with which I have met was that of a boy aged seven years, in whom, owing to an abnormal rotation of the bowel, the duodenum was twisted sharply around the mesenteric vessels with resultant recurring attacks of complete duodenal obstruction which brought him frequently to the point of death.

* Read at Cleveland before the Inter-State Post-Graduate Assembly, October, 1926.

These attacks were finally stopped by short-circuiting the bowel around the difficulty. Any factor which allows of an undue drag on the mesentery may lead to duodenal compression. Congenital or acquired visceroptosis allowing of the small intestines sinking into the true pelvis without resting on the pelvic floor, a mobile proximal colon which sags into the pelvis and exercises traction on the mesentery, loss of supporting fat and defective bodily posture; all tend in greater or less degree to make the duodenal exit narrow and the passage of its content precarious. Chronic inflammatory fibrous thickening of the root of the mesentery, tuberculous adenitis and progressive or retrograde infiltration of the mesenteric pedicle by malignant disease, have all in my experience been the causative factors in producing a chronic duodenal ileus. Whatever the obstructive factor, dilatation of the first three parts of the duodenum is the striking feature. Hypertrophy of the wall may be encountered; it is, however, in my experience, not the rule. The pylorus is almost always widely patent and the stomach dilated. When the transverse colon is thrown upward the abdomen appears empty, the small intestines lying in the pelvis; the third part of the duodenum, however, bulges forward into the wound in unmistakable prominence.

Associated Lesions. Duodenal ileus would appear to predispose to ulceration in the stomach and duodenum. Out of 75 cases in which the dilated duodenum was exposed, in 12 cases one or more ulcers were present in the duodenum, in 4 cases a gastric ulcer was found, and in 3 cases both gastric and duodenal ulcers were present; that is, in 19 cases out of 75, or in 25 per cent of cases, there was coincident ulceration. In 4 cases, all in females, there was coincident cholecystitis with gall stones.

Sex and Age Incidence. Of the 75 cases with which I have met, 23 were in males, 52 in females. The average age at the time of operation was thirty-eight years in the males, forty-one years in the females; the youngest patient a boy, aged seven years, the oldest a man, aged sixty-six years.

Symptomatology. The clinical picture in this condition, while characteristic in the pronounced cases, is often ill-defined and difficult to differentiate. The one symptom to which I find constant reference made in the case records is epigastric fulness and flatulence coming on a short time after meals. As this symptom is also common to gall bladder disease, confusion must frequently arise. Pain is usually complained of, starting about half an hour after food, and felt usually just to the left but sometimes to the right of the umbilicus. Vomiting is not a constant symptom; when it does occur it is usually in periodic bouts, recurring every four or five weeks and lasting for from twenty-four to forty-eight hours at a time. Such attacks are described as severe bilious attacks. They are ushered in by malaise, headache and complete

loss of appetite. The vomiting is repeated and copious, bilious in character and leaves the patient weak and prostrated. Rapid improvement and a longer or shorter period of relief follows such an attack. Not infrequently these attacks date back to early childhood and are regarded as constitutional or as evidence of recurring acidosis. Such attacks may disappear during late adolescence and the patient may enjoy comfort for ten or fifteen years, when there appear the flatulent symptoms which bring the patient to seek relief. This late reappearance of symptoms may follow child-bearing, some illness, such as influenza, or periods of mental worry associated with deficient muscular exercise and fresh air, in fact with any condition which tends to lower the tone of the abdominal muscles and to favor visceroptosis.

Some patients discover that by adopting the recumbent position and raising the pelvis the discomfort and feeling of distention are relieved, a few state that they have found that kneeling and lowering the shoulders allows the flatulence to pass on. The persistence of the symptoms, the failure of dietetic measures to relieve them, the dread of eating induced by the inevitable discomfort which follows, all tend to make the patient nervous and frequently neurasthenic. The primary symptoms may come to be obscured by others of reflex or purely nervous origin, and the history in such cases is very difficult to assess and to disentangle. Further, the condition may be complicated by duodenal or gastric ulcer or both, or by biliary disease with a resultant symptom complex, hard to evaluate.

Physical Signs. The patient is usually spare and of slender build with narrow costal angle and broad pelvis. The stomach is found to be low, often dilated and splashing. Definite epigastric fulness may be visible at the time of examination. Splashing and gurgling in the duodenum may be elicited. It is exceptional to find, however, and I have been able to demonstrate it in only 4 cases. Definite tenderness is found in the majority of cases at some point, either just to one side of or above the umbilicus. Palpation of the lower part of the abdomen may determine the presence of a large dilated cecum in some cases.

Roentgen Ray Evidence. One might reasonably imagine that a hold up of the barium meal in the duodenum would be the inevitable and necessary evidence of a duodenal ileus. In the majority of cases it is so, and the dilated duodenum, outlined by its opaque content, is best seen about one and a half hours after ingestion of the meal. A fairly characteristic picture is to see, four hours after a barium meal, a saucer-like residue in the dilated first and third portions of the duodenum. In some cases, however, where recurrent attacks of sickness form the outstanding feature in the history, a Roentgen ray examination in one of the intervals of freedom may fail to show anything suggesting a real duodenal obstruction. Undoubtedly the most satisfactory results, following operative treat-

ment, have been in those cases in which there was obvious Roentgen ray evidence of duodenal stasis.

Differential Diagnosis. Duodenal ileus is most liable to be confused with gall-bladder trouble, and in many of my earlier cases the abdomen was opened with a diagnosis of cholecystitis. The use of cholecystography has narrowed the margin of error very considerably. In a number of cases a wrong diagnosis of duodenal or gastric ulcer had been made. The frequency of coincident ulcer and ileus, however, makes the differential diagnosis none the easier.

Operative Diagnosis. The problem of diagnosis is by no means always solved once the abdomen is opened. In the pronounced case, where the widely dilated pylorus and bulging first portion of the duodenum immediately present in the wound, and where on throwing up the transverse colon the abdomen appears empty but for the dilated third part of the duodenum which rises to the level of the abdominal wall, there is little difficulty in recognizing the trouble or determining the line of treatment. In not a few cases, however, where the symptoms and signs have been merely suggestive and where a visceroptosis, with a moderate dilatation of the duodenum, is the only abnormality discoverable, the surgeon is in two minds as to the diagnosis and as to the propriety of performing a duodenojejunosomy. It is in such cases that the demonstration of a definite obstruction by the root of the mesentery is so difficult and uncertain. The methods of inflating the stomach and duodenum by passing air through a stomach tube with the parts exposed to view, which I practised at one time, I have now discarded as the evidence which it gives is, I believe, untrustworthy. In 21 such doubtful cases I have performed the operation of duodenojejunosomy. The result has been very good in 5; in 8 cases the patients have been much improved and in the remaining 8 cases the patients still complain of their old symptoms.

Treatment. So many factors and pathologic conditions may result in duodenal stasis that no one line of treatment is suitable for all. In the common type, where visceroptosis is the primary cause, conservative and postural treatment will relieve or cure a considerable number of patients. The importance of postural treatment on the lines so ably worked out and practised by Goldthwaite, alone or combined with operative treatment, cannot be too strongly emphasized. I have had the benefit of the assistance of Mr. W. A. Cochrane, a pupil of Goldthwaite, in the management of some of my cases, and I have been greatly impressed with the results of his postural methods. Many cases, however, are seen too late to be cured by physical measures, short of operation, and in these the performance of a duodenojejunal anastomosis is, I believe, the operation of choice. Where a mobile proximal colon has sagged into the pelvis a colopexy may give relief but is not as

certain as where a duodenal anastomosis is carried out. Where the duodenal obstruction is due to an infiltration of the mesenteric root by simple inflammatory, tuberculous or malignant disease a duodenojejunostomy is the only rational operation.

Duodenojejunostomy. This operation, first suggested by Barker and Bloodgood and first performed by Stavely, I have carried out in 64 cases of duodenal stasis. The operation is easy to perform in the suitable case; difficulty of access usually means a questionable indication. The anastomosis may be made either submesocolic antiperistaltic or transmesocolic isoperistaltic. In the majority of cases the former is the more suitable; in some, however, the dilated second part of the duodenum, reached through the transverse mesocolon, presents itself more readily for anastomosis. In my series there were 57 submesocolic antiperistaltic and 7 transmesocolic isoperistaltic operations. No appreciable difference in the after results could be found in the two series. Whichever operation is performed a free mobilization of the duodenum is desirable. Angled clamps may be employed but lately I have discarded the use of clamps in many cases. In all but the first few cases, No. 00 twenty-day catgut or the eyeless needle has been used for both layers of sutures.

In a number of cases the duodenojejunostomy was associated with other procedures. In 5 cases with duodenal ulcer a gastroenterostomy was also performed, in 1 case a gastroduodenostomy. In 1 case where old gastric and duodenal ulcers had caused hour-glass contractures of stomach and duodenum a gastrogastrostomy and a gastroduodenostomy were performed as well. In 4 cases a coincident cholecystectomy was performed and in 1 case a cholecystectomy and choledochotomy. These multiple procedures were well tolerated and did not contribute to the mortality.

Postoperative Treatment. In the asthenic and visceroptotic type of patient, so prominent in the duodenal ileus group, the operation of duodenojejunostomy, when necessary, should form only an incident in the course of treatment. After the immediate convalescence from operation the patient should wear a suitable abdominal belt and should undergo a course of postural treatment, which will effect an immense benefit, both to the abdominal condition and to the general tone and morale. I confess that in many of my cases too little care was given to the after-treatment and in such cases, after a temporary improvement, a recurrence of symptoms was reported.

The immediate result of the operation is, as a rule, eminently satisfactory. Little postoperative trouble is encountered and the mortality is low. In this series of 64 cases there were 3 hospital deaths. In 1 case a very feeble patient, who had suffered from persistent vomiting after a gastroenterostomy performed two years previously, the patient died two weeks after the operation from

peritonitis, following a rupture of the abdominal wound with prolapse of the intestines. In a second case the patient died from shock following an extensive resection of the small intestine for tuberculosis; a duodenojejunostomy was performed as well, as the duodenum was greatly dilated from pressure by glands at the root of the mesentery. In the third case the patient suffered from exophthalmic goiter. Persistent bilious vomiting for three months was attributed to pressure on the duodenum by calcareous tuberculous glands in the root of the mesentery shown by Roentgen ray. The patient recovered from the abdominal operation but died after a subsequent operation on the thyroid while still in hospital. The dilatation of the duodenum in this case was not very great and the abdominal operation was ill advised and undoubtedly had a malign influence on the thyrotoxicosis. It must, therefore, be included in the mortality list. A fourth death might also with some reason be included, that of a patient who died of pneumonia two weeks after leaving hospital. In spite of these deaths, all of which occurred in cases complicated by other trouble, the operation may be ranked as one of the safest in abdominal surgery. The convalescence is, as a rule, smooth and uneventful, more so than in the case of gastroenterostomy.

Ultimate Results of Duodenojejunostomy. The cases dealt with in this paper were all operated upon between February, 1921, and July, 1926. In more than half of them periods of from three to five and a half years have elapsed since operation. A recent *questionnaire* as to their present state has given the following facts:

Excluding 7 cases, 3 of which were not traced and 4, which, although well, are too recent for comparison, there remain 57 cases. Of these 23 patients reported that they were cured of their former trouble, had gained in weight—1 as much as 49 pounds—had no vomiting or digestive trouble. In 11 cases the patients reported themselves as very much improved, although having occasional flatulence and pains. In 12 cases the report was of improvement tempered with occasional digestive trouble. In 9 cases there was either little improvement or relapse after a temporary benefit. In this latter group of unsatisfactory cases were included the marked visceroptotics, some of whom had had several previous operations, and in whom the operation of duodenojejunostomy was performed in the hope that it might benefit, although the indications for it were somewhat indefinite.

The best results were undoubtedly in those cases where, prior to operation, there was definite roentgenologic evidence of duodenal stasis. Where associated with gastroenterostomy for duodenal ulcer with ileus, the results were uniformly good. In 3 cases in which secondary duodenal ileus was caused by malignant infiltration of the root of the mesentery, the primary growth being in the lesser curvature of the stomach, great relief was given for periods of

from four and a half months to seven and a half months, when death resulted from widespread disease.

Conclusions. In reviewing this group of cases one finds that where the duodenum was found at operation to be obviously obstructed by some more or less gross anatomic abnormality or pathologic process in the root of the mesentery, the results of a short-circuiting operation were excellent. Where the duodenum was found dilated, but no very obvious obstructing cause was visible, the short-circuiting operation gave most uncertain results. In many, an early improvement was followed by recurrence of symptoms. In no case, however, was the patient made worse by the operation.

A dilatation of the duodenum may apparently be present without any detectable mechanical obstruction, for reasons as yet unknown, and the drainage operation in this class of case is relatively ineffective. In the visceroptotic individual with signs of duodenal ileus, postoperative physical and especially postural treatment is essential for complete and lasting relief.

ACUTE INTESTINAL OBSTRUCTION: MECHANISM AND SIGNIFICANCE OF HYPOCHLOREMIA AND OTHER BLOOD CHEMICAL CHANGES.

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No surgical problem has caused more controversy than intestinal obstruction. None has been more thoroughly studied. Yet, if any one fairly familiar with the recent literature on this subject will read Kocher's¹ paper published in 1898, he will be astonished by how little our knowledge has increased in the last thirty years. There is still no agreement among authorities as to the cause of death in acute intestinal obstruction.

The problem has proved to be extremely complex. For many years it was attacked as a whole, as if there were but one type of obstruction and one cause of death. This narrow viewpoint has hindered progress. Recent writers have begun to modify it. Of late much attention has been devoted to the changes in blood chemistry found in acute intestinal obstruction. This paper is a report of an investigation covering this phase of the subject.

Historical Review. McCallum and coworkers² in a series of experiments, begun as early as 1909, called attention to the relationship between gastric tetany and pyloric obstruction. They found the mechanism to be an increased alkalinity of the blood, and a marked reduction of the plasma chlorids due to the loss of hydrochloric acid through vomiting. More recently Haden and Orr³ have made a valuable contribution to our knowledge by pointing out that these same changes occur in acute obstruction of the small intestine. They have shown that there occurs a marked fall in blood chlorids and a subsequent increase in the urea and total nonprotein nitrogen, this increase being greatest in the last twenty-four hours of the animal's life. Accompanying the fall in chlorids there is a marked increase in the carbon dioxid combining-power of the plasma (alkalosis). These changes are more pronounced in duodenal or high intestinal obstruction.

Our own observations have shown that these results can be duplicated repeatedly by following the technique outlined by Haden and Orr. In their interpretation, however, Haden and Orr⁴ have chosen to assume that the fall in blood chlorids is due not to a loss or output of chlorids, but to a fixation in the tissues of the chlorin ion with a toxin from the obstructed bowel. This utilization of the chlorin ion they regard as a protective mechanism on the part of the body. The terminal increase in the nitrogenous elements of the blood, coming as it does after the chlorids are reduced, is, according to their views, an evidence that this protective mechanism has been exhausted.

They⁴ support their views by reporting dogs with obstruction of the duodenum kept alive for twenty to thirty days by frequent hypodermic injections of solutions of sodium chlorid, whereas untreated controls died in from three to seven days. In their treated animals the other chemical elements of the blood remained normal as long as the chlorid level was maintained in this way.

Foster and Hausler⁵ strongly attack the views of Haden and Orr. They maintain that the marked changes observed in the control animals of Haden and Orr occurred in the first five days, before the tissues damaged by the operation had time to heal. Foster and Hausler have reported two dogs with obstruction at the duodenum produced by cutting and inversion of the bowel under local anesthesia. These animals were then given physiologic salt solution hypodermatically during the first five days to tide them over this critical period of repair. Complete food, water and salt starvation was then begun. The animals lived a total of twenty-one and twenty-eight days respectively.

From this, Foster and Hausler concluded that death in uncomplicated cases of acute intestinal obstruction is due to dehydration and starvation, that there is no evidence of toxemia, and that hypochloremia is not present. Their statement concerning the blood chemistry we cannot substantiate.

We wish, however, to emphasize a view held by Foster and Hausler that there must be recognized two types of acute intestinal obstruction: (1) Acute simple obstruction in which there is complete blocking of the lumen with no circulatory involvement; (2) acute strangulation in which there is interference with venous, arterial and lymphatic circulation as well as obstruction to the intestinal lumen. The morbid processes involved and the symptoms thereof are widely different in these conditions. For these reasons, if for no other, the complex problem under the general term intestinal obstruction is merely made more confusing by any writing which does not differentiate these mechanisms. Obviously in most of the conditions which are designated as acute intestinal obstruction the actual mechanism is acute strangulation. Gall stones, enteroliths or other foreign bodies may completely occlude the lumen of the small intestine without the factor of strangulation but these form a relatively small percentage of cases. In all the commoner forms of obstruction such as volvulus, intussusception, hernia, twists or kinks, and adhesion bands, it is the strangulation and the ensuing gangrene which contribute most of the factors leading to death. In a later publication we shall hope to evaluate and coördinate these lethal factors. The present writing will be confined to the changes in the blood chemistry which occur in each form of acute intestinal obstruction.

Procedure. Dogs were employed in all experiments. The operations were performed with aseptic technique under morphin and ether anesthesia. Hausler⁶ and Foster have criticized the use of these drugs, claiming that the first five days after operation constitute a critical period during which time the control animals die because they have to combat, not only the obstruction but also the anesthetic and the tissue damage of the operation. While there is some merit in this contention we feel that they have overemphasized it. Dogs withstand ether anesthesia and abdominal surgery remarkably well. Great numbers of dogs recovering from intestinal anastomosis may be taken as controls of this fact.

One animal we purposely subjected to a long anesthetic, during which time the duodenum was divided and a lateral anastomosis done, an awkward operation causing much trauma and tending to produce a bad functional result. This animal (Dog 41) recovered promptly, never vomited at any time and showed no changes in blood chemistry.* Since this dog served as a general control we give the blood chemistry in Table I.

* The chemical analysis of our experiments were conducted by W. S. Fisher in the Department of Biochemistry, Indiana University School of Medicine, under the supervision of Dr. B. B. Turner and Dr. R. N. Harger. Urea nitrogen in the blood was determined by method of D. D. van Slyke and G. E. Cullen (*J. Biol. Chem.*, 1914, 19, 211). Total nonprotein nitrogen by method of Folin and Wu (*J. Biol. Chem.*, 1919, 38, 81). Sodium chlorid in the blood by method of Whitehorn (*J. Biol. Chem.*, 1921, 45, 449). Sodium chlorid in the urine and vomitus output by a slight modification of the same method. Total nitrogen in the urine by method of Folin and Denis (*J. Biol. Chem.*, 1916, 26, 473).

TABLE I.

(Dog 41. Division of the duodenum with lateral anastomosis.)

Remarks.	Day.	Mg. per 100 cc. blood.			Urine output.	
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	Quantity, cc.	NaCl, gm.
Day of operation	0 . .	9.6	29.8	568		
No food or water	1 . .	14.5	34.9	534	320	3.12
No food or water	2 . .	15.0	40.2	536	300	2.17
Water <i>ad lib.</i> and milk	3 . .	14.1	40.0	547	170	0.27
Water <i>ad lib.</i> and milk	5 . .	10.2	30.3	503	1100	0.76
Water <i>ad lib.</i> and milk	7 . .	16.1	40.0	546	1070	3.30
Animal at large	56 . .	15.6	36.6	490		

It will be noted that this animal continued to excrete sodium chlorid in the urine normally for two days despite the fact that no food, water, or salt was given during this period. There was only a slight reduction of blood chlorids. This may be due, no doubt, to the fact that there was an abundance of salt in his gastrointestinal tract at the time of operation. Also, due to dehydration, the actual decrease would be concealed by a moderate concentration in his blood. On the third day the excretion of chlorids fell practically to *nil*. With the administration of water there was a marked increase in urine but yet practically no excretion of chlorids. The blood chlorids, however, showed a more pronounced fall due to the proper dilution of the blood. Then with the administration of milk, the blood and urine chlorids regained their former level. The animal was at large in the pens two months, at the end of this time there were no abnormal or significant changes in blood chemistry.

In all, 54 dogs were used. After testing various methods of producing obstruction, the plan of dividing the bowel and inverting the ends was finally adopted to produce an acute simple obstruction. In the study of obstruction plus strangulation various methods were employed as will be described later.

The Reduction of Blood Chlorids and the Increase in Nonprotein Nitrogen. At the outset let us state that we soon discovered the changes in blood chemistry to be largely dependent upon the postoperative course of the animal. Our findings varied chiefly according to whether or not the dog was given water. We can, perhaps, present our observations most clearly in the form of a series of propositions to each of which is appended the supporting experimental evidence.

1. *There is usually no appreciable decrease in blood chlorids until after forty-eight hours. Thereafter the reduction is greater the*

longer the animal lives without the administration of salt. The reduction of blood chlorids is directly proportional to the chlorids lost by the animal, which occurs chiefly through vomiting. The loss through vomiting is greatest in dogs allowed water by mouth *ad lib*.

The following protocols give data which is typical of our findings under the conditions described. No effort was made to control the food or water intake of these animals before operation. The preoperative dose of morphin however always produced vomiting which emptied the stomach of any grossly undigested food. The animals were kept in metabolism cages in which the total output of urine and vomitus could be collected.

Dog 37.—Obstruction of the duodenum; no water, food or salt given. The animal showed no signs of tetany, but died at the end of sixty-five hours in a state which seemed due chiefly to dehydration. Autopsy showed a superficial wound infection and distention of the duodenal stump, in which there was some discoloration. The chemical findings are given.

Dog. 38.—Obstruction 12 inches above the cecum. No food, water or salt given. In this animal also there were no demonstrable symptoms of tetany. He died at the end of sixty-nine hours in much the same condition as Dog 37, a "toxic" state with frequent vomiting of brownish fluid in small quantities, the heart rapid and bounding and extremities pulseless. Autopsy showed acute simple obstruction, but with some distention and discoloration of the proximal stump. There was no actual gangrene and no peritonitis. The findings are given in the table.

TABLE II.

(Intestinal obstruction; water withheld.)

Remarks.	Day.	Mg. per 100 cc. blood.			Vomit.		Urine.	
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	Quantity, cc.	NaCl, gm.	Quantity, cc.	NaCl, gm.
Dog 37 (obstruction at duodenum; water withheld)	0 . . .	10.7	37.7	515				
	1 . . .	4.9	36.5	482	1010	6.76		
	2 . . .	36.4	65.5	432	320	2.40		
	3 . . .	87.2	142.8	440	200	1.50		
						2.60*		
	Total	13.26		
Dog 38 (obstruction of ileum; water withheld)	0 . . .	8.3	28.2	523				
	1 . . .	6.1	33.3	450	770	4.10	130	0.52
	2 . . .	23.5	66.2	392	610	5.04		
	3 . . .	50.9	117.6	384	490	4.16		
						2.30*		
	Total	15.60	...	0.52

* Washings from pen.

Dog 36.—Obstruction at the duodenum in the same manner as Dog 37. Water allowed by mouth *ad lib.* There was no other treatment. The symptoms displayed by this animal were much different from those seen in animals which had no water. This dog drank much water and vomited it freely. For the first sixty to sixty-four hours postoperative his condition remained good. Then he began showing signs of tetany, first a rigor of the jaw in attempting to drink, and a stiffness of the legs. At seventy hours tetany was marked, there were constant twitchings and spasms of all the muscles, breathing was slow and dehydration was marked. At seventy-nine hours the animal was rigid and prostrated, respirations were very rapid and shallow, becoming slow and superficial toward the end. Rigor mortis was present when the dog died at the end of eighty hours. Autopsy showed acute simple obstruction of the duodenum, with no evidences of peritonitis; all parts of the bowel normal in color, the upper segment only slightly distended. (See Table III.)

Dog 42.—Obstruction 12 inches above the cecum. Given water by mouth *ad lib.* The postoperative course and symptoms were similar to those of Dog 36. This animal lived about ninety-two hours. The autopsy showed simple complete obstruction of the ileum, with no complications. (See Table III.)

TABLE III.

(Intestinal obstruction; water *ad lib.*)

Remarks.	Day.	Mg. per 100 cc. blood.			Vomitus.		Urine.	
		Urea nitrogen.	Total nonpro- tein nitrogen.	NaCl.	Quan- tity, cc.	NaCl, gm.	Quan- tity, cc.	NaCl, gm.
Dog 36 (obstruction of the duodenum; water by mouth, <i>ad lib.</i>)	0 . . .	14.70	40.5	482				
	1 . . .	6.10	32.9	450	350	3.25	150	0.75
	2 . . .	13.80	58.2	351	2950	12.68	60	Trace
	3 . . .	38.50	130.0	246	1360	5.79		
	4 . . .	88.60	165.6	205				
						2.11*		
	Total	23.83	...	0.75
Dog 42 (obstruction of ileum; water by mouth <i>ad lib.</i>)	0 . . .	13.25	40.2	490				
	1 . . .	9.20	41.6	419	1250	4.20		
	2 . . .	7.50	29.3	434	1550	4.65		
	3 . . .	11.84	45.1	389	730	3.00		
	4 . . .	62.90	95.2	278	800	2.05		
						3.40*		
	Total	17.30		

* Washings from pens.

From these experiments it will be noted that a large excretion of chlorids ensues promptly with the vomiting. With some effort the urine and vomitus were collected in separate ends of the cages in a sufficient number of cases to assure us that in these obstructed animals the quantity of urine excreted is small, and the chlorids

lost in that way are negligible. The vomiting, however, has always produced a definite loss of chlorids, greatest in those animals allowed water *ad lib.* These dogs will literally wash out their chlorids by drinking and vomiting large quantities of water and their reduction of blood chlorids is correspondingly greater. Dog 37, (Table II), showed a loss of 13.26 gm. of sodium chlorid, and at death his blood contained 440 mg. of sodium chlorid per 100 cc. Whereas, Dog 36 (Table III), allowed water *ad lib.* by mouth, lost 23.83 gm. and reduced his blood chlorids to 205 mg. per 100 cc. In all of these animals dehydration was marked.

These animals have all shown a greater output of chlorids than has been reported by Haden and Orr. We believe that this may be due entirely to the chlorid intake just previous to operation. They report that in their animals food was withheld for forty-eight hours previous to operation, whereas, in this series there was no preoperative starvation. This would undoubtedly alter the chlorid content of the bowel at operation, and we feel that it accounts for the discrepancy in our findings. Dog 41 (Table I), in which there was no obstruction and no preoperative starvation, excreted in the urine more than 5 gm. of sodium chlorid in forty-eight hours without appreciable change in the chlorid content of the blood. The excretion then fell off sharply, being resumed again when food was taken. As opposed to this, Dog 28 (Table IV), which was starved for twenty-four hours, obstructed at the duodenum, and allowed water by mouth *ad lib.*, died after seventy-two hours, having reduced the chlorids to 351 mg. with an output of only 6.67 gm. Obviously the amount of excess sodium chlorid possessed by the animal will modify the blood changes resulting from any loss which he may undergo.

TABLE IV.

(Dog. 28. Starvation for twenty-four hours preoperative; obstruction of the duodenum; water by mouth, *ad lib.*)

Day.	Mg. per 100 cc. blood.			Vomit and urine.	
	Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	Quantity, cc.	NaCl, gm.
0	8.6	35.5	489	.	
1	7.7	52.5	442	330	1.87
2	37.2	107.1	368	1251	2.50
3	77.4	203.4	351		2.30*
Total	6.67

* Washings from pen.

It appears that in the starving animal the chlorids quickly reach a level of equilibrium with little or no reserve. In such a case a relatively small loss causes a reduction of blood chlorids. This loss is quickly accomplished by vomiting, in the obstructed animal where the hydrochloric acid secreted by the stomach has no chance for reabsorption. A potential loss may even be accomplished without vomiting if this chlorid laden secretion is retained in the obstructed stomach and upper bowel. We have repeatedly analyzed the contents of the obstructed bowel for sodium chlorid, finding 700 to 900 mg. per 100 cc. In this connection it is interesting to note that obstruction at the sigmoid causes neither vomiting nor reduction of blood chlorids.

Dog 34.—Obstructed at the sigmoid by cutting and inversion of the bowel. Water was allowed by mouth *ad lib.* There was no other treatment. There was no vomiting, and the animal's condition remained good for six days. Toxic symptoms then set in with fever, prostration and circulatory collapse. At autopsy on the seventh day all the intestinal loops were markedly distended, and there were patches of discoloration along the antimesenteric border. There was no peritonitis.

TABLE V.

(Dog. 34. Obstruction at the sigmoid; water, *ad lib.*)

Day.	Mg. per 100 cc. blood.			Urine.	
	Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	Quantity, cc.	NaCl, gm.
0	6.4	22.0	495		
1	9.4	45.5	388	530	2.45
2	6.8	43.1	445	180	0.33
4	8.1	27.8	462	260	0.26
6	6.4	37.0	465	325	0.24
7	9.6	44.0	460		
					0.50*
Total	3.78

* Washings from pen.

In an obstruction of this type, the intestinal contents pass beyond the cecum where the absorption of the sodium chlorid together with the water may take place. As shown in Table V, there is, under these conditions, no loss of chlorids by vomiting and no hypochloremia, even though the obstruction be fatal.

In high intestinal obstruction there is usually a slight hypochloremia apparent at the end of the first day, but the reduction is not appreciable until after forty-eight hours. We have never observed tetany in these animals until after the sodium chlorid in the blood has fallen to a level of 350 mg. per 100 cc. Though we regard such a reduction of chlorids as a lethal factor, we do not feel that it bears any relationship to the "toxemia" of intestinal obstruction.

Certainly there is no evidence that the chlorids are fixed in the tissues by a toxin. In several dogs we have analyzed the liver and muscle tissue for chlorids⁷ always finding a reduction comparable to the hypochloremia. It is probable that similar changes would be found in other tissues.

TABLE VI.
(Chlorids in the tissues.)

	Grams of NaCl per kg.	
	Liver.	Muscle.
Normal Dog A	3.23	0.95
Normal Dog B	3.22	1.05
Dog 37 at death	2.45	0.79
Dog 36 at death	1.00	0.36

In none of our experiments have we encountered evidence to indicate that the hypochloremia of acute intestinal obstruction results from any cause other than a loss of chlorids. This loss is accomplished by the retention of chlorids in the upper intestinal segment and by vomiting. The amount of chlorid loss necessary to cause hypochloremia depends upon the chlorid reserve which the animal has at the time of obstruction.

2. *A reduction of blood chlorids as marked as that which occurs in acute intestinal obstruction can be produced by the ligation of both ureters or the removal of both kidneys.*

Our data on nephrectomized dogs is given in Table VII.

TABLE VII.
(Blood chemistry in nephrectomy and intestinal obstruction; effect of sodium chlorid.)

Remarks.	Day.	Mg. per 100 cc. blood.		
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.
Dog 19 (bilateral nephrectomy; obstruction of the bowel 12 inches above cecum; profuse vomiting and convulsions on last day)	0	2.9	16.2	449
	1	61.9	100.0	439
	2	180.0	222.0	266
Dog 22 (ligation and division of both ureters; water by mouth, <i>ad lib.</i> ; profuse vomiting; death in four days)	0	9.6	28.0	530
	1	54.5	67.0	509
	2	120.0	162.0	468
	3	169.7	214.0	425
	4	192.7	277.0	359
Dog 23 (bilateral nephrectomy; water by mouth, <i>ad lib.</i> ; profuse vomiting and convulsions on last day)	0	18.8	32.0	469
	1	64.9	79.9	491
	2	106.2	171.0	400
	3	156.5	198.0	298
Dog 24 (bilateral nephrectomy; water by mouth, <i>ad lib.</i> ; daily hypodermoclysis of 2 per cent NaCl solution; profuse vomiting; no convulsions observed)	0	14.1	34.8	521
	1	55.5	65.0	552
	2	71.0	139.0	500
	3	151.3	170.0	442
	4	178.0	270.0	531

In all of these animals there was frequent vomiting and a great reduction of blood chlorids. Dog 19, in which there was intestinal obstruction as well as double nephrectomy, showed a more rapid course, but the changes in blood chemistry were identical with those seen in the animals with nephrectomy only. The administration of 2 per cent salt solution to Dog 24 maintained for him a normal level of blood chlorids but had no effect on the increase of nitrogenous elements. Though unfortunately the chlorid output was not measured in these animals, we feel that here again the hypochloremia must be due to the loss through vomiting.

3. *Dogs with acute simple obstruction may be kept alive throughout the period of starvation by the hypodermic administration of sodium chlorid and water, but this treatment is of little or no value in cases of acute strangulation. The administration of salt to an animal with acute obstruction is of no avail if water is withheld.*

Haden and Orr have repeatedly demonstrated the value of solutions of sodium chlorid in acute intestinal obstruction, but we feel that the mechanism and limitations of this therapeutic effect need as adequate explanation.

Dog 44.—Obstruction at mid-duodenum. No food or water allowed. Ten grams of NaCl in 30 cc. of water injected hypodermically eighteen hours postoperative. Injection painful. Twenty-four hours later the same injection was repeated intravenously. Autopsy showed simple uncomplicated obstruction of the duodenum.

Dog 45.—Obstruction at the mid-duodenum. No food or water allowed. At the end of eighteen hours 10 gm. of NaCl was given intravenously in 30 cc. of water. On each succeeding day one-half that amount was given. Blood samples were drawn before and five minutes after the injection the first two days; on the third day the second blood sample was drawn at death, eight hours after the last injection of salt. Autopsy showed simple uncomplicated obstruction of the duodenum.

Dogs 35 and 40.—In these dogs a 12-inch loop of lower ileum was isolated by cutting and anastomosis of the bowel around it. The ends of the loop were inverted, the mesentery of loop was ligated and cut allowing the segment of lie free in the abdominal cavity. Dog 35, which received no treatment, died in sixteen hours. At autopsy the loop was in a state of anemic gangrene, foul smelling and of a pale brown color. The structures of the omentum and bowel, against which it had been lying, were gangrenous. All of the abdominal structures were inflamed, but there was no pus. Dog 40, which received a total of 2000 cc. of normal salt, lived twenty-five hours. Autopsy showed the loop almost entirely destroyed by the gangrenous process. There was generalized peritonitis.

In explaining the therapeutic effect of sodium chlorid Haden and Orr have assumed a specific neutralization of the toxins. They have shown that no other inorganic salt possesses this power to save the animal, and have also shown the administration of fluids without sodium chlorid is of no avail.

TABLE VIII.

(Obstruction of ileum 12 inches above the cecum; water by mouth, *ad lib.*; treatment as indicated in remarks.)

Remarks.	Day.	Mg. per 100 cc. blood.		
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.
Dog 18 (allowed water by mouth, <i>ad lib.</i> , but no salt; tetany developed rapidly; autopsy on third day showed acute simple obstruction of the ileum)	0	12.3	22.4	579
	1	11.6	27.9	416
	2	13.0	23.1	257
	3 8 A.M. . .	22.8	75.9	228
	2 P.M. . .	61.5	103.7	211
Dog 17 (given daily by hypodermoclysis a total of 1000 to 2000 cc. of 1.8 per cent NaCl solution; dog in good condition; no toxic symptoms; on nineteenth day, under local anesthesia, an attempt was made to relieve the obstruction by enterostomy; the whole small intestine was thickened, but there was no strangulation or marked distention; death on twenty-first day from generalized peritonitis, as a result of the enterostomy)	0	9.2	20.6	560
	1	6.1	23.8	495
	2	6.2	20.1	486
	3	5.9	26.7	521
	4	5.5	16.6	521
	5	4.2	21.9	471
	6	4.4	16.9	512
	7	5.3	25.0	516
	8	4.1	19.1	535
	10	5.4	20.3	477
	12	6.3	20.1	481
	18	5.8	20.8	454
	21	7.4	23.3	830
Dog 26 (given water, <i>ad lib.</i> , by mouth, and 1000 to 1500 cc. of 2 per cent NaCl solution daily; autopsy on second day showed gangrene and perforation of the lower 2 inches of the obstructed bowel)	0	6.6	21.2	537
	1	4.2	24.1	504
	2	5.2	32.6	628
Dog 32 (1000 cc. of 2 per cent NaCl solution daily; condition good for six days; autopsy on seventh day showed great distention and discoloration of the lower 12 inches of the obstructed bowel; no actual gangrene)	0	13.7	48.0	466
	2	11.5	34.3	537
	4	10.7	34.5	478
	7	20.9	122.0?	468

All of their findings we have been able to substantiate, but we do not feel warranted in assuming any detoxifying action. Copher and Brooks⁸ have shown that the contents of obstructed bowel are very toxic, causing death when injected intravenously. Also that animals receiving the injection show no changes in blood chlorids, and cannot be saved by the administration of salt solution. We have found it easy to prolong life in the animals with duodenal obstruction by the administration of sodium chlorid and water. In obstruction of the ileum, however, we have been able to accomplish this only once in our series. Dog 17 (Table VIII) responded to this treatment, whereas Dogs 26, 32 and several others were lost by the same treatment. Always where the treatment failed there

was found to be some damage to the bowel wall by overdistention or strangulation. This complication occurs much less readily in obstruction of the duodenum.

TABLE IX.

(Obstruction at midduodenum; water withheld; daily injection of saturated salt solution, as given in protocols.)

Remarks.	Day.	Mg. per 100 cc. blood.		
		Urea.	Total nonprotein nitrogen.	NaCl.
Dog 44:	0	13.6	36.8	513
Before injection	1	10.2	37.9	412
Before injection	2	63.0	91.4	468
After injection	3	60.9	98.8	637
Dog 45:	0	12.0	41.4	469
Before injection	1	10.3	35.5	400
After injection	1	9.5	34.7	579
Before injection	2	17.6	39.7	524
After injection	2	17.6	42.2	613
Before injection	3	31.8	54.6	614
After injection	3	45.0	80.0	724

TABLE X.

(Complete strangulation of 12 inches of ileum; treatment as indicated in remarks.)

Remarks.	Day.	Mg. per 100 cc. blood.			Vomit and urine.	
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	Quantity, cc.	NaCl, gm.
Dog 35 (no treatment; profuse vomiting)	0	7.5	34.2	502		
	1	6.4	44.4	335	650	6.44
Dog 40 (1000 cc. 0.9 per cent NaCl)	0	5.3	39.2	523		
	1 2 P.M. . . .	7.2	36.4	542		
	1 11 P.M. . .	21.0	75.0	523		

We feel that in acute simple obstruction the intact mucosa of the intestine prevents absorption of the toxins from the lumen, hence there is no toxemia.⁹ There is, however, rapid dehydration, loss of chlorids through vomiting and starvation. These in the order named are the lethal factors in acute simple obstruction. The giving of sodium chlorid solution by hypodermoclysis prevents death from dehydration and hypochloremia. However, with the slightest degree of strangulation the absorption of toxins ensues,

and the treatment with salt does not prevent death from this toxemia (Table VIII).

It is not our intention to underestimate the importance of sodium chlorid in the animal body under these or any other conditions. It is quite apparent that a proper concentration of this salt in the blood and tissues is indispensable in maintaining the normal osmotic relations and the entire fluid metabolism of the body. In those animals with a marked reduction of the chlorids, the blood becomes thick and dark, and we have found no means other than the administration of sodium chlorid *and water* by which this severe dehydration and other symptoms of hypochloremia can be prevented or relieved.

It is apparent also that the course of a toxemia, such as occurs in acute strangulation of the bowel, may be mitigated by transfusions of sodium chlorid solution as will be seen by a study of Table X. This action must be due to the support of the general circulation and to an increased elimination through the kidneys. The fact that the administration of sodium chlorid is of no avail if water is withheld would seem to disprove a specific detoxifying action (Table IX).

As additional proof of our interpretations the following experiment is cited.

Dog. 30.—The bowel was cut at the mid-duodenum and 12 inches above the cecum. The duodenum was then anastomosed to the ileum and the ends of the loop thus isolated were inverted, converting practically the entire small intestine into an obstructed loop with the lumen of the bowel reëstablished around it. The animal was allowed water, *ad lib.*, by mouth. For five days there was no other treatment. The dog vomited profusely, and on the fifth day was in tetany and very near death. Treatment, by hypodermoclysis, with sodium chlorid, was instituted as indicated in Table XI. Symptoms were promptly relieved, and for two days his condition remained good. On the third day there were unmistakable signs of toxemia. The wound was in bad condition on account of great abdominal distention, and since the animal was practically moribund, he was sacrificed. At autopsy the large obstructed loop was found enormously distended and there were areas of beginning gangrene along the antimesenteric border. There was no peritonitis or other complication. The chemical findings are given in Table XI.

It is apparent in Table XI, that Dog 30 developed symptoms of hypochloremia only on the fifth day. This fall in chlorids is less rapid than we have seen in animals with simple obstruction, yet in this animal the whole small bowel was converted into an isolated loop filled with toxic fluids. The difference is due, no doubt, to the fact that his intestinal lumen was not blocked. In spite of his vomiting, a part of his stomach secretion passed on into the large bowel. His symptoms on the fifth day were relieved promptly by a hypodermoclysis of 2 per cent salt solution. Three days later, though his blood chlorids remained above the normal level, a fatal toxemia

developed as a result of damage to the wall by overdistention and strangulation. Previous to that time the intact mucosa had prevented the absorption of these toxins.

TABLE XI.

(Obstructed loop; duodenum anastomosed to ileum; water, *ad lib.*, by mouth; treatment as indicated in remarks.)

Remarks.	Day.	Mg. per 100 cc. blood.			Vomit and urine.	
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	Quantity, cc.	Grams.
No treatment	0	15.6	47.6	465		
No treatment	1	11.6	38.5	449	860	2.5
No treatment	2	16.6	39.7	425	1160	2.8
No treatment	4	15.6	51.3	359	1540	2.8
1000 cc. 2 per cent NaCl	5 10 P.M. .	34.1	68.9	321	750	1.4
1000 cc. 1 per cent NaCl	6	16.4	57.0	643	1310	3.3
	8	10.8	37.0	736	4860	14.5
						4.8*
	Total	32.1

* Washings from pen.

TABLE XII.

(Dog. 39. Obstruction of the duodenum; treatment as indicated in remarks.)

Remarks.	Day.	Mg. per 100 cc. blood.			Vomit and urine.	
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	Quantity, cc.	Grams.
1000 cc. 1 per cent NaCl*	0	9.4	37.9	531		
1000 cc. 1 per cent NaCl*	1	3.0	28.9	490	1360	12.12
1000 cc. 1 per cent NaCl*	2	9.6	37.7	457	980	8.50
1000 cc. 1 per cent NaCl*	3	9.8	18.9	506	460	2.15
1000 cc. 1 per cent NaCl*	4	14.8	42.5	507	715	6.44
No food; water, salt	6	16.4	36.6	543	1250	11.80
No food; water, salt	8	19.4	48.0	523	240	0.30
No food; water, salt	10	23.5	46.5	523	450	3.10
No food; water, salt	12	46.4	69.7	490	890	9.80
						5.00†
	Total	59.21

* Hypodermically.

† Washings from pen.

We believe that in acute simple obstruction, experimentally produced, the actual course is exaggerated by the absorption of toxins through the damaged tissues in the inverted stump of the bowel. The two dogs of Foster and Hausler,⁵ to which we have

previously referred, demonstrate this fact. Dog 39 (Table XII) of our series was obstructed at the duodenum and allowed water *ad lib.* for five days. During this time he received 5000 cc. of a 1 per cent solution of sodium chlorid by hypodermoclysis. Thereafter all food, water, and salt were withheld. The dog continued in good condition until the twelfth day, dying, apparently, of inanition. Autopsy showed uncomplicated simple obstruction.

Though this dog did not live sufficiently long to furnish a striking demonstration, the results are in keeping with those of Foster and Hausler. If hypochloremia and dehydration are prevented for the critical period of the first five days, the animal, with simple occlusion of the intestinal lumen, may then exist throughout the period of inanition without food, water or salt. The loss of chlorids by vomiting under such conditions will be slight because the starving stomach secretes very little hydrochloric acid.

From a careful analysis of our results it becomes evident that death in acute simple obstruction is not due to toxemia. We have no evidence that a high level of blood chlorids prevents death from an existing toxemia and we see no reason for assuming a specific detoxifying action by sodium chlorid. The hypodermic administration of sodium chlorid solution has a specific therapeutic value in acute intestinal obstruction in that it overcomes the hypochloremia and the dehydration, both of which are lethal factors in this condition.

4. *The relationship between hypochloremia and the terminal increase in nonprotein nitrogen is not definite.* We have found that a marked fall in blood chlorids is always followed by a rapid increase in the concentration of the nitrogenous elements. In pointing to this relationship Haden and Orr have assumed it to be a definite indication that the obstructed bowel brings about a toxemia which fundamentally involves the chlorids. In our experience, however, this increase has often occurred in dogs with a normal blood chlorid level. The truth of this will be apparent from a study of the tables.

It will be observed in Tables VIII and IX, that animals, receiving large quantities of fluid by hypodermoclysis, show even at death very little accumulation of nitrogen in the blood; but animals, in which dehydration is allowed to occur show the increase in spite of normal blood chlorids. We have tried a number of experiments in an effort to separate these two factors. Dog 25 constitutes one experiment of this type.

Dog 25.—Ileum was obstructed 12 inches above the cecum and the distal segment was brought up into an enterostomy wound. The dog was allowed water, *ad lib.*, and at frequent intervals given an enteroclysis of tap water. By this means 800 to 1200 cc. of water daily was given into the bowel below the obstruction. The dog vomited freely, but remained in good condition for five days. On the sixth day he was markedly dehydrated and in tetany. Autopsy on this day showed distention of the whole

lower bowel and discoloration of the terminal foot of the ileum. There were no other complications.

TABLE XIII.

(Dog 25. Obstruction of the ileum with enterostomy into distal segment. Water by enteroclysis; no salt.)

Remarks.	Day.	Mg. per 100 cc. blood.			Vomit and urine.	
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	Quantity, cc.	NaCl, gm.
Good condition for five days	0 . . .	10.5	35.7	497		
	1 . . .	6.2	22.2	480	1320	4.55
	2 . . .	3.2	28.8	462	1830	0.55
	3 . . .	4.9	31.4	439	2420	0.42
	4 . . .	8.6	36.4	363	1370	1.12
	5 . . .	12.2	40.8	363	1290	2.18
	6 . . .	16.4	71.4	295	690	1.61
						4.16*
	Total	14.59

* Washings from pen.

This animal was one in which we devoted much effort toward the placing of fluid in the lower bowel where absorption might take place. Dehydration was not marked till after the chlorids were greatly reduced. In this dog the increase in nonprotein nitrogen was relatively slight. The actual degree to which dehydration will ordinarily occur in obstructed animals allowed water *ad lib.* by mouth is shown in Table XIV.

TABLE XIV.

(Dog 52. Obstructed at mid-duodenum; water, *ad lib.*; no other treatment.)

Day.	Mg. per 100 cc. blood.			Blood.		Vomit.		Urine.
	Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	R. B. C.	Moisture.	Quantity, cc.	NaCl, gm.	
0 . . .	10.5	37.7	436	7,900,000	76.9			
1 . . .	5.6	31.9	436	8,900,000	73.8	690	4.2	
2 . . .	44.4	52.6	345	10,100,000	69.4	3370	4.9	
3 . . .	54.2	173.9	329	13,800,000	65.2	4450	2.8	
Total	11.9	

We have found it practically impossible to maintain the water balance in a dog with a marked degree of hypochloremia. It is

certain that the obstructed animal becomes dehydrated in spite of taking large quantities of water by mouth, and this dehydration becomes absolute as the chlorid level falls. In this state the excretion of urine is practically *nil* and we believe this the chief explanation of the rapid terminal increase in blood nitrogen.

In support of our views on this effect of dehydration we offer the findings in two dogs (Nos. 29 and 27).

Dogs 29 and 27.—Both were starved and caused to vomit twice daily by the hypodermic injection of apomorphin. One of them, Dog 29, was allowed, just previous to the administration of apomorphin, a limited quantity of water. From the other, Dog 27, all water was withheld.

TABLE XV.

(Starvation; vomiting induced twice daily by apomorphin.)

Remarks.	Day.	Mg. per 100 cc. blood.			Vomit and urine.	
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	Quantity, cc.	NaCl, gm.
Dog 29 (water in limited quantities)	0	16.2	71.8	504		
	2	9.1	39.7	490	940	2.50
	4	13.3	38.0	452	1290	2.20
	5	21.9	40.0	415	460	0.97
	6	16.5	43.5	407	110	0.18
	8	15.3	48.0	393	215	0.41
	10	17.9	43.0	408	140	0.28
	20	20.5	48.4	421	1530	2.00
Released	26	7.7	52.4	442	660	0.76
Dog 27 (no water)	0	12.8	33.3	530		
	1	12.6	31.9	530	680	3.42
	2	15.6	41.4	483	300	1.37
	3	13.2	46.1	492	220	0.60
	4	21.2	70.5	514	130	0.50
	5	29.3	106.8	515	116	0.20
	6	37.8	135.0	520	120	0.90
Died						

In neither of these animals did vomiting produce a large output of chlorids or a marked reduction of blood chlorids. Obviously vomiting which is not excessive and not associated with obstruction of the intestine will bring about no permanent disturbance in the secretion and reabsorption of chlorids. In Dog 29, which was allowed water, there was an appreciable fall in the blood chlorids but there was no nitrogenous accumulation in the blood when the dog was released on the twenty-sixth day. Dog 27, with no change in chlorids, died in six days and showed the rise in nonprotein nitrogen which we have found to occur always in fatal dehydration. Our findings indicate that the relationship which appears to exist between hypochloremia and the blood nitrogen increase of acute

intestinal obstruction is explained best on the basis of dehydration. A profound reduction of blood chlorids rapidly intensifies the already existing dehydration; there results a marked impairment of kidney function and a rapid accumulation of nonprotein nitrogen in the blood. This increase may also be due in part to increased tissue destruction from dehydration.

Early in our efforts to differentiate the factors of salt and water we verified the fact reported by Haden and Orr⁴ that the hypodermic administration of water alone to an obstructed dog causes death sooner than no treatment whatsoever. This apparently astonishing fact was made more readily understandable when we discovered a similar administration of water to a normal dog to be rapidly fatal. Later we made a more careful study of this observation, and two such animals are reported herewith.

TABLE XVI.

(Dogs. 53 and 54. No water by mouth; hypodermic administration of distilled water as indicated in the remarks.)

Remarks.	Day.	Mg. per 100 cc. blood.			Blood.		Urine.		
		Urea nitrogen.	Total nonprotein nitrogen.	NaCl.	R. B. C.	Moisture, per cent.	Quantity, cc.	NaCl, gm.	Total nonprotein nitrogen, gm.
Dog 53 (distilled water)									
500 cc.	0 . .	15.8	44.3	490	6,900,000	78.9			
500 cc.	1 . .	8.1	32.4	468	6,000,000	79.2	365	0.27	4.73
500 cc.	2 . .	8.5	34.8	445	6,100,000	80.4	380	0.43	6.27
1000 cc.	3 . .	7.7	33.9	480	5,100,000	81.2	295	0.14	5.61
500 cc.	4 . .	9.8	29.9	490	4,800,000	82.4	650	0.31	6.50
Died	5 . .	51.2	62.5	430	...	85.2	50	0.05	0.60
Dog 54 (distilled water)									
1500 cc.	0 . .	10.7	45.9	513	7,000,000	79.8			
1500 cc.	1 . .	25.7	74.1	435	395	2.05	6.17
Died	2 . .	45.1	96.8	356	...	72.3	110	0.56	2.26

The exact mechanism of death from the administration of water is not clear. There is marked hemolysis of the red cells and this may be the explanation. The points which we wish to emphasize at this time are the lowered excretion of urine and the rapid terminal increase in blood nitrogen which resulted. This mechanism operated more rapidly in Dog 54, which received the large injections of water. It is interesting to note that this animal showed a reduction of blood chlorids which cannot be explained by his output. In this case the

chlorids have been drawn rapidly into the water-logged subcutaneous tissue. Unfortunately a second red cell count was not obtained on this animal but the determination of the total moisture in the blood showed an actual dehydration in the face of more than 2000 cc. of excess water in the subcutaneous tissue.

We regard this as a striking indication that a normal water and salt balance is essential in maintaining the kidney function as well as the entire metabolism of the body. The administration of salt alone is of no value if water is withheld. The parenteral administration of water alone is fatal.

Conclusions. 1. In acute simple obstruction of the small intestine where the bowel wall remains intact, death is not due to toxemia. The lethal factors are dehydration, reduction of blood chlorids by vomiting, and starvation. Administration of sodium chlorid and water by hypodermoclysis or any method which preserves the salt and water balance, will prolong life through the period of starvation.

2. In acute strangulation of the bowel the factor of toxemia is added. Treatment with sodium chlorid and water does not prevent death from this toxemia.

3. The increase in the nonprotein nitrogen of the blood appears to result chiefly from dehydration and a rapid reduction of kidney function. Hypochloremia is an important factor in this mechanism. It is also possible that hypochloremia and dehydration cause increased tissue destruction which adds to the nitrogenous increase.

4. For these reasons, the administration of physiologic sodium chlorid, by hypodermoclysis or intravenous transfusion, will be a valuable procedure in the treatment of intestinal obstruction and gastric tetany.

5. Since strangulation of the bowel occurs in most cases of obstruction, the limitations of the treatment are obvious.

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CLINICAL CAUSES AND DIAGNOSTIC AND PROGNOSTIC
SIGNIFICANCE OF JAUNDICE.*

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HERBERT SPENCER says in one of his books, I think in *First Principles*, that mankind in its progress passes through three stages, the unanimity of the ignorant, the disagreement of the inquiring, the unanimity of the wise. Upon most questions in medicine we are still in the first stage, upon many in the second, upon none in the third. It was while thinking about jaundice that this expressive dictum of Herbert Spencer came to my mind. Up to a very recent period, as time goes, we were in comfortable agreement that jaundice was twofold, obstructive and toxic; the former due to gross obstruction of the outflow of the bile, the latter due to excessive destruction of red cells and consequently greater manufacture of bile by the obliging liver—all jaundice was therefore hepatogenous. The second period of our progress was not long in coming. It was shown by Virchow and others that a substance identical with bilirubin could be formed from extravasated blood outside of the liver. This led many to the conviction that bile was made both in the liver and outside of the liver. When at a later period, however, Minkowsky and Naunyn showed in experiments on birds that after the removal of the liver bile was no longer formed bilogenic monopoly was again restored to the liver.

Then came Aschoff and his pupil McNee,¹ and demonstrated, or seemed to demonstrate, that bile production was the property of certain large endothelial cells widely scattered through the body and identical with the stellate cells of Kupffer in the liver. To these endothelial cells found in the liver and in the spleen, in the lymph nodes, bone marrow, and so forth, Aschoff gave the name of reticuloendothelial system, and to this system he and his followers ascribe the property either of making bilirubin out of disintegrated or dead red cells or of preparing such cells for conversion into bilirubin by the liver.

Whipple and Hooper afterward showed that in the dog whose liver had been excluded from the circulation bile pigment was still formed and appeared in the blood.

Among the last and most important investigations in this field are those of Mann, Bollman, and Magath,² of the Mayo Clinic, who succeeded in extirpating the liver from dogs and keeping the animals alive for from twenty-four to thirty-six hours, a longevity never before attained. In such anhepatic dogs they found that

* Part of Symposium on Jaundice before the American Gastro-Enterological Association, May 5, 1926; containing also a report of some cases of epidemic jaundice.

bilirubin continued to be formed. Their observations were soon confirmed by Rich³ and Makino.⁴

But scarcely had the work of Mann, Bollman and Magath been published when the conclusions drawn from it were challenged by Melchior, Rosenthal and Licht,⁵ of Breslau. Repeating in general the technique of Mann and Magath, they tested the bile-forming power of the hepatectomized dogs with toluylendiamine and phenylhydrazine, which in control dogs produced marked icterus. They found that after the removal of the liver no appreciable icterus followed the injection of the poisons.*

As the matter stands today, insofar at least as the experimental evidence is concerned, no definite proof has been brought that bile is chiefly formed outside of the liver, in the so-called reticulo-endothelial system, or of the fact, a corollary of the first, that the liver is merely an excretory organ for bile made elsewhere, as the kidney is for urea, with the formation of which it is in nowise concerned.

Nevertheless, I am inclined to believe, on clinical grounds, that bile can be formed extrahepatically. I have seen jaundice in cases of large fatty liver, the acute yellow hypertrophy of Rolleston, in which under the microscope scarcely an intact polygonal cell remained. The sections had all the appearances of areolar fatty tissue and could be recognized as of liver origin only by the presence of bile ducts.

Perhaps one more point should be mentioned in support of the theory of Aschoff and McNee and other recent experimenters as to the formation of bile outside of the liver, namely, the fact that van den Bergh and Gansslen, Zipperlen and Schüz⁶ have found more bile pigment in the blood of the splenic vein than in that of the splenic artery, the spleen being as we know one of the most important constituents of the reticuloendothelial system.

I have gone into these few details because in the obscure field of clinical jaundice every datum of scientific research bearing upon the probable seat of bile formation is helpful to a better understanding.

The Clinical Causes of Jaundice. The classification proposed by van den Bergh into mechanic and dynamic is, in the main, satisfactory but perhaps a little too rigid. McNee has lately suggested a modification which is not unlike that of older writers and which helps I think to clarify the subject. McNee, an ardent reticulo-

* Aschoff, in a recent article (Klin. Wchnschr., 1926, 5, 1260) published after the present paper was written, takes issue with the Breslau experimenters and insists that their researches do not disprove the observations and conclusions of Mann and Magath. As regards the nondevelopment of jaundice in hepatectomized dogs after toluylendiamin and phenylhydrazin injections, Aschoff is of the opinion that the repeated glucose injections necessary to keep the dogs alive, may have had a share in preventing icterus. In any event the work of Mann and Magath proves the intravascular formation of bile pigment outside of the liver-cell.

endothelialist, distinguishes: (a) Obstructive hepatic jaundice; (b) toxic and infectious hepatic jaundice; (c) hemolytic jaundice.

(a) **OBSTRUCTIVE HEPATIC JAUNDICE.** The clinical causes of obstructive hepatic jaundice, mechanical jaundice, are, in the main, the following:

1. Obstruction by stone or other foreign body in the common bile duct. This is one of the most frequent and most easily understood types of jaundice. Before the introduction of the van den Bergh test it was supposed to occur in about 10 per cent of cases of gall stone—at least, that was the surgeon's figures. I found it more frequent when, instead of asking only about the color of the skin, I also inquired as to the color of the urine.

The van den Bergh test has shown the great frequency of moderate bilirubinemia in many cases of biliary colic in which there is no visible jaundice and no choluria.

2. Through tumor of the bile ducts or of the head of the pancreas; also through pressure upon the ducts by large glands, by aneurysm of the hepatic artery, and so forth.

3. Through stricture of the duct as a result of scar formation.

4. Through inflammation of the mucosa of the duct with the formation of a mucous plug. This is the commonly accepted explanation for so-called catarrhal jaundice; however, no one it seems has ever found such a plug in acute catarrhal jaundice. More probably we are dealing in catarrhal jaundice with a cholangitis and mild hepatitis, or with acute swelling of the head of the pancreas analogous to mumps.

5. Through traction on the bile ducts by a floating kidney.

6. Through injuries—cutting of the bile ducts during operation. Jaundice under these conditions appears almost immediately, is permanent painless, but accompanied by intolerable itching, thus simulating the jaundice due to malignant obstruction.

7. Passive congestion of the liver in chronic heart failure. I am placing this in the group of obstructive jaundice although the mechanism of congestive jaundice is by no means clear. The obstruction of the ducts if it exists, is intrahepatic.

8. Cirrhosis of the liver. Here, too, whatever obstruction exists is intrahepatic, but other factors cannot be ruled out.

9. Carcinoma of the liver with intrahepatic or extrahepatic pressure.

In many cases of what appears to be purely mechanical or obstructive jaundice, for example, that due to a stone blocking the common duct, the liver is the seat of degenerative and inflammatory changes, of a hepatitis which may become a not easily evaluated factor both in the jaundice and in the general clinical picture.

(b) **TOXIC AND INFECTIOUS HEPATIC JAUNDICE.** This group comprises types of jaundice in which there is no gross mechanical obstruction in the extrahepatic ducts, barring an occasional excep-

tion to which I shall refer. Bile is present in the urine and in the feces. By the van den Bergh test the blood serum is said to give a delayed direct as well as a negative direct reaction (biphasic reaction, McNee).

Illustrations of this type of jaundice are:

1. *Weil's Disease*. This is now known as Spirochetosis ictero-hemorrhagica or leptospirosis. The disease became prominent as a clinical entity during the World War, which brought confirmation of the finding of the *Leptospira icteroides* originally discovered by Japanese observers. A number of true cases of spirochetosis have been reported in this country, among them 2 by Sailer.⁷

The disease sets in with chill, headache and prostration; occasionally the onset is gradual. Nausea, vomiting, abdominal and muscular pains, jaundice and fever complete the picture. Sometimes in bad cases a peculiar odor manifests itself. The liver is enlarged; the spleen not constantly.

The causative parasite normally lives in the wild rat; it is highly pathogenic for guinea pigs and can be kept alive and virulent in them for an astounding number of generations. It is present in human blood until about the seventh day of the disease and in the urine up to the fortieth day or longer. It should be looked for in dark-field illumination.

Immune bodies appear in the blood of patients and can be produced experimentally in animals so that both cure and prophylaxis in times of epidemic may become feasible.

2. *Infectious Jaundice, Nonspirochetal*. This as a rule is a mild type of jaundice. It is most common in children, and has of late years prevailed in widely scattered sections of this country. After an incubation period of from eight to ten days the disease sets in abruptly with fever, constipation and abdominal pain. Jaundice appears in four or five days or later—up to the twentieth day—and lasts for from seven to ten days, although it may disappear in a few hours or continue for six weeks.

The disease resembles acute catarrhal jaundice, indeed sporadic cases would undoubtedly be so diagnosed. Except for a milder course and absence of mortality, it is similar to Weil's disease, but the most careful search by Blumer, Wadsworth and Noguchi has failed to show any leptospira.

During the last few weeks we had a small outbreak of epidemic jaundice in Philadelphia. The 3 following cases occurred in one family:

Case Reports. CASE I.—P. D., aged thirteen years, was seized on the evening of April 13, 1926, with high fever and headache. The fever continued on the next day and nausea appeared. On the following day there was no fever but persistent nausea and some vomiting, with a crop of hives and much itching. On April 17 the eyeballs were yellow. The stools were pale but not putty colored; the urine contained considerable bile. There

was a slight enlargement of the liver, not of the spleen, and no abdominal tenderness.

CASE II.—S. D., aged twelve years, started on April 15, 1926, two days after her sister, with similar but milder symptoms. Her jaundice was slight although bile was readily demonstrated in the urine. When last seen, on May 2, there was still a faint tinge to the conjunctiva.

CASE III.—E. D., aged fifteen years, a third sister, was taken ill suddenly on April 19, 1926, four days after the second case, with no other symptom than fever (up to 104° F.) which continued for forty hours. On April 25, after she had been well four days, but still in bed, she became distinctly jaundiced and had pronounced general itching. There was also some vomiting.

It is interesting that having had routine examinations of the urine made in all three cases, bile was detected in the third patient's urine before the color of the eyeballs attracted attention.

In another case, also a young girl, which I did not see, but about which I was consulted, careful search was made for leptospira by Dr. Lynch, of the Pepper Laboratory, with negative results.

Such cases as those here described are in the beginning usually called grippe or influenza—often abdominal influenza—during the period of apparently causeless fever, nausea and vomiting. The subsequent discovery of jaundice is considered a sequel or a complication. I believe the whole process is a unitary disease due to some obscure transmissible infection which with the modern technique should not elude us for long.

While epidemic jaundice is a mild disease, it seems to bear a relation to acute yellow atrophy or acute degenerative hepatitis, as is shown by the following case:

CASE IV.—Dr. A. E. F., aged fifty-two years, a man in perfect health, was seized with jaundice, which in the course of two weeks became very intense. There was no pain at any time, only great prostration. The urine was black and the stools in the beginning were clay colored. When I first saw the patient, I concluded, not finding a palpable gall bladder, that I was dealing with one of those rare cases of silent stone or with a toxic hepatitis. Two days after my visit to him in his home town, he was brought to the Hospital of the University of Pennsylvania. He had a deep canary color, no fever, no tenderness and was apathetic, almost stuporous. The liver was not enlarged, perhaps it was a trifle smaller than normal; the spleen was not palpable. A somewhat striking feature was a peculiar body odor like that of fresh laboratory meat broth. Two days later he died in coma, our diagnosis being acute degenerative hepatitis. Autopsy showed complete freedom from disease on the part of the gall bladder and bile ducts but advanced degeneration of the liver. Both during life and after death careful search was made for spirochetes, but with negative results.

Now, there is in connection with this case a most interesting and suggestive fact which I ascertained prior to the man's death. Dur-

ing the few weeks before he fell ill, there had been an epidemic outbreak of jaundice in his community. He had attended from 18 to 20 cases, 5 of them being in one household. One cannot escape the belief that an infection was at work and that the doctor had received through his multiple contacts such an intensive dose of the poison that he developed what is comparable to an acute yellow atrophy of the liver.

I am trying to obtain some rats from the place where the jaundice has prevailed, but if the observations of Blumer and other investigators are borne out, our results will be negative.

3. *The Jaundice of Infectious Diseases.* Typhoid fever, pneumonia, septicemia, and so forth.

As a rule, the jaundice of pneumonia is a mild complication, but in rare instances it is severe and darkens the prognosis greatly. The sputum in the grave cases is a bright green color due to biliverdin. If one may use the van den Bergh reaction as a basis, the jaundice of pneumonia is in part due to an active hemolysis and in part to a toxic hepatitis.

4. *Toxic Jaundice.* Particularly that due to arsphenamin, chloroform, and so forth.

Much discussion has arisen as to whether the jaundice occurring after arsphenamin injections is syphilitic, that is, due to the *Treponema pallidum* or to gummatous lesions or to a toxic effect of the arsenic. If to either of the first two one might be inclined to push the arsphenamin; if to the last, nothing would be more harmful (Gordon and Feldman⁸). Blood bilirubin studies have shown that in certain cases the bilirubin content is increased when arsphenamin is given, long before any icterus is manifested externally. If the use of the drug is continued the bilirubinemia becomes more marked and finally, the threshold being passed, jaundice appears. It is due to a degenerative hepatitis which is best combated with glucose. If the van den Bergh test is regularly made in cases receiving the arsenicals the drug will be discontinued and glucose will be given as soon as the icterus index begins to mount and before severe liver damage has taken place (Gerrard⁹).

5. *Postoperative Jaundice.* I have already spoken of this as a possible consequence of trauma to the bile ducts during operation, but there is yet another type of postoperative jaundice—that in which there is an infective cholangitis or a septic thrombophlebitis of the portal vein. This type of jaundice is most frequent as a sequel of operations on cases of suppurative appendicitis and possesses a rather well-defined clinical physiognomy. Jaundice sets in a few days after operation, early in the development of the infection. (It can occur also in cases of appendicitis not operated upon.) Fever is present with chilly sensations, high leukocytosis, tenderness over the liver and localized edema. Lassitude, anorexia and emaciation are striking symptoms. The patients often remark

that "they are too tired to sleep." The Roentgen ray is of value in the diagnosis.

(c) **HEMOLYTIC JAUNDICE.** The term hemolytic jaundice* (ictero-anemia) connotes a jaundice due to blood destruction and not to primary disease of the liver cells or any part of the liver. That at least is the meaning given to the term by the majority of French writers and by Minkowski, a German pioneer in this field. On the other hand, Naunyn and his followers, while attributing the jaundice to excessive blood destruction, believe that excessive amounts of pigment made in the liver cause the formation of thrombi in the bile capillaries. On that basis the jaundice would be the result of an intrahepatic obstruction. However, the newer researches on the origin of bile pigment strongly point to the possibility, as indicated in an earlier part of this paper, of an extrahepatic source for bile pigment, though perhaps not the only source. It is therefore probable that hemolytic jaundice is independent of obstruction of the bile capillaries.†

The blood destruction occurs chiefly in the spleen, liver, lymph nodes and bone marrow; but with respect to some of the conditions belonging under the head of hemolytic jaundice we have little knowledge of the place of blood destruction.

Two types of hemolytic jaundice are recognized: (a) The acquired type (Hayem-Widal); (b) the congenital or familial (cholémie familiale) (Chauffard-Minkowski). In both, far greater amounts than the threshold value of 4 units of bile pigment may be present in the blood without bile appearing in the urine—hence the synonym, acholuric jaundice. In most cases the bile is excreted as urobilin in increased amounts in the feces and also in the urine.

A number of features are common to both types:

1. There is a chronic jaundice, with the presence of bile pigment in the blood serum, but without bile in the urine (acholuric jaundice).
2. The signs of biliary obstruction are absent—there is no itching, no bradycardia, no clay-colored stools.
3. There are no bile salts in the blood.
4. Anemia is common to both types, but is more marked in the acquired, reaching at times as low a figure as 1,000,000 red cells.

* For a full discussion of this subject see Pearce, Krumbhaar and Frazier (*The Spleen and Anemia*, Philadelphia and London, 1918) and Meulengracht (*Der chronische hereditäre hämolytische Icterus*, Leipzig, 1922).

† Dr. I. S. Ravdin calls my attention to an interesting statement by Riolanus, Jr., indicating that as far back as the seventeenth century a distinction was made between obstructive and nonobstructive jaundice. Riolanus (*A Sure Guide or the Best and Nearest Way to Physick and Chirurgery*, translated by Nicolas Culpepper, 1691) says: "When I see in an extremely yellow jaundice the whole skin infected with choler and that the urine dye cloths yellow, the stools being in the meantime whitish, and when I see in another sort of jaundice both urine and stools yellow, this confirms to me that there are two forms of choler and several ways for the expurgation of them."

5. The spleen is enlarged and firm.
6. Urobilinuria, an indication of blood destruction, is present.
7. Fragility of the red cells. This sign, first pointed out by Chauffard, is found in both types but is more marked in the congenital or familial than in the acquired. Normally, hemolysis in hypotonic salt solution begins at 0.42; in hemolytic jaundice it begins even as high as 0.6.

Blood regeneration is evidenced by an increase of reticulocytes.

8. Splenectomy is usually curative.

While the cases viewed in a large way fall into two groups, congenital or familial and acquired, the differences are scarcely fundamental and there are many borderline cases, as, for example, congenital cases with negative family history. Such cases are perhaps better classified with the acquired type.

Gall stones are quite common in familial or congenital hemolytic jaundice, but seem to bear no etiologic relation to the jaundice. In some cases, as pointed out in an admirable paper by Dutton,¹⁰ crises occur during which symptoms of obstructive jaundice are added to the clinical picture. These crises are attributed by Dutton to a heightened activity of the neuromuscular reflex apparatus of the bile passages (see also Hopkins¹¹).

In the acquired type acute exacerbations with deepening jaundice are frequent.¹² The acquired cases as a rule also present a severer clinical picture than the congenital. The latter, in Chauffard's words, are often more icteric than sick. A number of German writers¹³ have called attention to the frequent coexistence of tower skull (Turmschädel) with hemolytic jaundice.

One may place under the head of acquired hemolytic jaundice, the icterus found in pernicious anemia and allied conditions in which the van den Bergh test shows increased values of the icterus index but in which there is no choluria.

Pathogenesis. The fundamental fault in hemolytic jaundice is either some lesion of the blood, such as might be called a dystrophy of the red cells, or an anomaly of the spleen that endows it with an exaggerated hemolytic activity. Since splenectomy is a curative measure, the latter hypothesis seems more reasonable. The spleen of hemolytic jaundice is not alone spodogenous, as it is in health, but it also destroys red cells in increased numbers and prepares others for destruction.

Difficult to explain on the lienal theory, however, is the fact that after the removal of the spleen the osmotic resistance of the red blood corpuscles to hypotonic salt solution sometimes remains as before, or does not return completely to normal.

Familial hemolytic icterus behaves in its hereditary transmission as a dominant character.

Icterus Neonatorum. This is a type of hemolytic jaundice due to rapid blood destruction. It occurs in about 50 per cent of

infants. The blood gives a positive indirect but negative direct van den Bergh reaction.

A rare example is the familial type of jaundice of the newborn, a grave disease occurring less often in the children of the first and second pregnancies than in those of later birth. Those that recover often show permanent cerebral or cerebellar defects.

Dissociated Icterus. French writers, and Hoover and Blankenhorn in this country, have called attention to dissociated icterus, that is, one in which bile salts and bile pigment are separate and do not occur together in the blood or urine. They recognize: (a) An hepatic dissociated icterus in which bile salts and bile pigments are separately present in the plasma as the result of separate hepatic excretion into the blood; (b) a renal dissociated icterus in which the bile pigment alone is present in the plasma due to renal excretion of the bile salts. The subject is one requiring further investigation.

General Features of Jaundice. 1. Yellowish discoloration of the skin, of the mucous membranes and of the deeper tissues is the most striking feature of jaundice. It is to be looked for first in the conjunctiva, and in colored races on the inside of the lower lip, the blood being pressed out with a glass slide.

The color varies from a light lemon or canary yellow to light or dark orange or olive brown. The darkest types are seen in the most chronic cases of obstructive jaundice, although a dark color of the skin is not necessarily proof of a high degree of bilirubinemia. Tears, cartilage, nerves and muscle tissue do not show staining. Pneumonic sputum in cases of jaundice is often light green in color due to oxydized bilirubin.

2. Itching of the skin is one of the most distressing of all jaundice symptoms. It occurs in obstructive not in hemolytic or toxic jaundice. It may precede the icterus—preicteric itching—hence it is probably not due to the bile pigment, but to bile salts or other constituents of the bile. In bad cases of itching the skin is more or less covered with scratch marks and often shows infection.

Surgical drainage or cholecystoenterostomy almost immediately puts a stop to the itching long before the color has faded from the skin; this is another point in favor of the view that the itching is not due to the bile pigment.

Xanthoma occasionally forms in long-standing jaundice.

Some cases of jaundice have a peculiar odor like that of fresh meat broth. This is particularly true of icterus gravis and of spirochetal jaundice.

The blood serum normally is slightly bile stained, the amount of bilirubin present, as measured by the delicate van den Bergh test, being from 0.5 to 2 mg. in 100 cc. of blood (1 to 2,000,000 to 500,000). A false augmentation of color may be produced by the presence of considerable amounts of carotin or lutein derived from the diet.

I shall not give the details of the van den Bergh test.* It will suffice here to say that in this test Ehrlich's diazo reagent is added to the blood serum. Normally the bilirubin of the blood gives the so-called delayed direct or indirect reaction, while that in the bile gives the immediate direct reaction. In the case of the blood, the immediate development of a bluish-violet color indicates, in van den Bergh's opinion, the presence of an excess of normal bilirubin and is to be interpreted as signifying obstructive jaundice with the resorption of normally formed bile from the liver. If the addition of alcohol to the serum-diazo mixture causes a deepening of the color, or the appearance of the characteristic color when there had not been any before, the reaction, called positive indirect, is interpreted as being due to bile pigment that has not been acted upon by the polygonal cells of the liver, and hence the test is significant of hemolytic jaundice. Whether this sharp differentiation drawn by van den Bergh and by McNee is correct has not been proved; indeed the most recent researches throw doubt upon it.

Icterus Index. The icterus index, a term first used by Stetten, is based upon a colorimetric comparison of the depth of color of the blood serum and a standard solution of potassium bichromate, 1 to 10,000, as proposed by Meulengracht.† The depth of color is expressed by a number called the icterus index, the normal index ranging from 4 to 6. Bernheim has arranged the following table expressing the range of the icterus index.

Zone of hypobilirubinemia	2.3 to 4
Normal zone	4 to 6
Zone of latent jaundice	6 to 15
Frank jaundice	Above 15

All cases with an index above 15 show jaundice, but a yellow skin and sclera may persist for some days after the index goes below 15, because bilirubin disappears more rapidly from the blood than from the other tissues.

Value of the Icterus Index. By means of the index it is possible to detect latent jaundice, that is, a bilirubinemia without clinical icterus. In cases of colicky pains of indefinite nature the presence of latent jaundice points to a biliary origin. The index may be used to follow the changes in the degree of jaundice in patients with frank icterus. As pointed out by Snell,¹⁴ the test helps in the discovery of hepatic congestion in early myocardial failure, in the

* The following are among the more important references to this subject: Van den Bergh: *Presse méd.*, 1921, 29, 441. Van den Bergh and Snapper: *Deutsch. Arch. f. klin. Med.*, 1913, vol. 110. Meulengracht: *Arch. Int. Med.*, 1925, 35, 214. Stetten: *Ann. Surg.*, 1922, 76, 191. Bernheim: *J. Am. Med. Assn.*, 1924, 82, 291; *Arch. Path. and Lab. Med.*, 1926, 1, 747. Ravdin: *Am. J. Med. Sci.*, 1925, 169, 850; *Surg. Clin. North America*, February, 1926. Greene, Snell and Walters: *Arch. Int. Med.*, 1925, 36, 248. Greene, McVicar, Rowntree and Walters: *Arch. Int. Med.*, 1925, 36, 418, 542.

† This test has been advantageously modified by Bernheim, who has substituted a glass standard for the 1 to 10,000 potassium bichromate solution.

differentiation of hemolytic from other anemias, and in the early demonstration of jaundice due to obstruction in the common duct.

Bernheim has shown that in gastric ulcer there is a normal bilirubinemia, while in duodenal ulcer (except in cases with hemorrhage) there is a hyperbilirubinemia. The retention of bile may be due to an extending duodenitis or to a certain degree of hyperglobulia which has been found not infrequently in ulcer of the duodenum. In diabetes mellitus the icterus index is high—the lowest index in 41 diabetic patients was 7.5; the highest, 15, the average, 10. The severe cases showed the highest indexes.

Bernheim has pointed out a possible use of the icterus index in the prognosis of pneumonia. No case with a normal bilirubinemia ended fatally. Although death did not occur in all cases showing hyperbilirubinemia, in no fatal case was this condition absent. As in many instances it is not possible to foretell the outcome from the clinical aspect, it is desirable to make further tests of the icterus index in the hope that it may prove of use both in prognosis and in the choice of therapeutic measures.

Hypobilirubinemia, revealed by the icterus index, is found in cases of secondary anemia not due to blood destruction but caused by hemorrhage or by lessened production—conditions in which less hemoglobin is liberated. In Bernheim's series every case of secondary anemia with a red cell count below 3,000,000 showed hypobilirubinemia.

Carotinemia. This condition, described by Hess and Myers, and to which I have already referred, is due to the prolonged use of carrots and other vegetables, fruits, eggs, and other foodstuffs, containing yellow pigments (lutein, xanthophyll, carotin). It produces a high icterus index—Greene and his associates found it as high as 26. By chemical tests, either the van den Bergh or the Meulengracht, it is readily shown that the actual amount of bilirubin is not above normal. A feature differentiating carotinemia from icterus is its tendency to be more prominent on the thicker epithelium, such as the palms and soles.

I might add further that the indirect reaction of van den Bergh has helped in the detection of latent jaundice in pernicious anemia and dithionite anemia and, as pointed out on a previous page, in the recognition of latent jaundice due to the toxic action of arsphenamin.

One more blood change might be mentioned—Thewlis and Middleton¹⁵ have demonstrated the existence of a leukopenia in uncomplicated cases of catarrhal jaundice. They show that sometimes the leukopenia precedes the appearance of the jaundice.

The Urine in Jaundice. In obstructive jaundice the urine is bile stained, but often the intensity of staining varies in different voidings for reasons that are hard to find. In hemolytic jaundice the urine as a rule is not bile stained (acholuric jaundice).

Urobilin or urobilinogen appears in the urine in cases of jaundice in which obstruction, if present, is not total, so that some bile can get into the intestines and be acted upon by bacteria. Hence its determination has been suggested as a test to distinguish catarrhal jaundice from that due to carcinoma of the head of the pancreas or the common bile duct, as in the usual case of carcinoma no bile whatever enters the intestine, therefore none can be transformed into urobilin (Wallace and Diamond¹⁶).

In cases of severe or of long-standing jaundice albumin and bile-stained tubocasts are present in the urine. Leucin and tyrosin appear in the urine in acute yellow atrophy. They were not found in the case of fatal icterus gravis reported in an earlier part of this paper.

The Feces. The clay or putty-colored stools of jaundice due to extrahepatic obstruction are well known. Such stools are seen at times in cases of toxic jaundice, evidently through an associated intrahepatic obstruction. In cancer of the head of the pancreas the feces are pale and shiny, due in part to unabsorbed fat and in part to the absence of bile; they look like buckwheat-flour dough and spread out thinly on the floor of the vessel.

Other Effects of Jaundice. In true hemolytic jaundice the fragility of the red blood cells is increased. While normally the breaking up of the cells occurs at between 0.44 to 0.34 per cent saline solution, in hemolytic icterus it begins at 0.6 or even 0.7 and is complete at 0.5 per cent.

A *lessened coagulability* has long been known to occur in chronic jaundice and has been much dreaded by surgeons as a source of hemorrhage. Its causes are not well understood. Although calcium injections prevent postoperative hemorrhage in jaundice cases, there appears to be no special loss of calcium in the blood. It may be, as suggested by Snell, that in jaundice the calcium and the bilirubin enter into some sort of combination which virtually entails a lessened calcium content.

Metabolic Effects of Jaundice. Most common are subnormal temperature and slow pulse. Emaciation may develop rapidly in obstructive jaundice, even in the absence of malignant disease. I have seen extreme loss of flesh in nonmalignant obstruction.

Nervous Disturbances. The most distressing of these is itching, which in stone or in malignant obstruction may become more unbearable than pain. It robs the patient of sleep and contributes to his rapid decline. Irritability and mental depression may occur even in mild types of jaundice, while in toxic jaundice there may be muttering or agitated delirium, coma or convulsions.

Diagnosis. In approaching the subject of the diagnosis of jaundice, or rather of its causative condition, we may with profit follow the advice of Deaver and ask: "Is the jaundice painless or is it painful?"

Painful jaundice is usually due to mechanical causes, especially to stone, to cholecystitis or to cholangitis. In rare cases the jaundice of calculus is painless—the so-called silent stone. It is not necessary that there should be successive attacks of colic—one definite painful seizure is of great help in the diagnosis of calculous obstruction.

If the jaundice is painless, the possibilities are many—with clay-colored stools and choluria, the suspicion falls on the pancreas or some other nearby structure. The most valuable diagnostic feature of jaundice due to the disease of the pancreas is a large gall bladder (Courvoisier sign). By gentle palpation the gall bladder may be felt; often it can be seen to move under the skin during respiration if the examiner will sit at the patient's side, with his eyes almost on a level with the abdomen.

Glycosuria favors the diagnosis of pancreatic disease, but does not permit exclusion of disease of the bile passages or liver.

I have thought that itching appeared earlier in malignant than in calculous obstruction; and as I have stated, the itching may be preicteric.

The icterus index is of value. A variable icterus index speaks in favor of stone, a constant or increasing figure is most common in extraductal or noncalculous obstruction.

Referring once more to the large gall bladder, it should be stated that, while most common in cancer of the head of the pancreas, it is also found in carcinoma of the papilla. Mention should also be made of a possible source of error due to the occurrence of the so-called Riedel's lobe, an elongated linguete projection of the right lobe of the liver, sometimes found in gall stones. It may readily be attributed to tumor or a large gall bladder.

I shall not refer to the various functional liver tests which may possibly prove of value in the final differentiation of the causes of jaundice. At present the tests give us information of the state of the liver rather than of the causes of jaundice. Such information is, however, of value in forming a comprehensive judgment of the patient as a surgical risk. When carried to a greater state of perfection they will undoubtedly become part of our routine preoperative study of jaundice cases.

Prognosis. The prognosis of jaundice can be as little stated in a few words as the prognosis of fever. It depends on the cause, on the resistance of the patient and very often on the intelligence of the medical adviser and on the skill of the surgeon.

In the hemolytic forms of jaundice, barring the graver anemias and hemolytic poisons, the prognosis is favorable. Cure is often achieved by splenectomy.

Regarding the other types of jaundice, I would say that no form of obstructive jaundice should ever be taken lightly. It is always

possible for a jaundice of mild beginning to become grave, as the case of the doctor I have cited above so well illustrates.

Jaundice may affect the outcome of the operation done for its relief. One should hesitate to promise early recovery in any case of jaundice no matter how simple the contemplated operation may be. In some elderly persons—analogous to what happens at times to the kidneys after prostatectomy—a postoperative hepatic insufficiency develops. There is but little drainage of bile, the appetite is in abeyance, the patient is exceedingly languid and seems incapable of making a fight for his recovery. Death may ensue in three or four weeks despite active treatment. It is probable that not only the liver but also the pancreas has a share in the disastrous outcome.

Under the use of calcium chlorid intravenously by the Walters method hemorrhage has been practically eliminated as a danger after operation upon jaundice cases. The prophylactic and post-operative use of glucose solution has lessened the incidence of liver disfunction or nonfunction. Nevertheless, I am of the opinion that in the presence of jaundice it behooves the surgeon to limit his interference to the essential minimum. I have seen lives sacrificed through the operator's eagerness to correct all pathologic defects in the abdomen. It is probable that the liver function tests will eventually make operations safer.

The prognosis is also influenced by the state of the other organs, particularly of the kidney and of the heart. A closer relationship exists between the kidney and the liver than is appreciated or is explainable in the light of our present knowledge. As for the heart, the prognosis is not so vitally affected by its condition if that be not too serious. In fact when the history permits the decision that the bile duct tract disease antedates the heart trouble, then we may conjecture that the gall bladder disease may be responsible for the disease of the heart and that operation may not only cure the disease of the biliary passages but also that of the heart as well.

In no other circumstances is it so important to take a comprehensive view of a patient's powers of resistance as in cases of jaundice that require operation. The laboratory tests, as I have stated above, are of value not only with respect to the jaundice itself, but also in throwing light on the functional capacity of the liver, kidneys, heart and pancreas. But in the last analysis the best judgment is reached by him who has had a large clinical experience and uses it wisely.

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CHOLECYSTOGRAPHY AND LYON-MELTZER TEST IN A PATIENT WITH A CONGENITALLY ABSENT GALL BLADDER.

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THIS article is brought before the medical profession, not so much on account of the infrequency of the congenitally absent gall bladder as for its substantiation of the value of cholecystography and for the light it throws on the source of Lyon's B bile. There are also included observations on the diabetic's postoperative intraabdominal adhesions on differences of medical and surgical procedure and on the way to proceed in clearing up questionable diagnosis of perinephritis and subdiaphragmatic abscess.

Case Report. G. S. a female, aged forty-eight years, born in Russia, was admitted to the Medical Service of Unity Hospital, December 5, 1924. Her chief complaint on admission was pain in the right upper abdomen and cramps. Since 1922 she had had several attacks of severe pain in the right hypochondrium which radiated toward the back. These attacks increased in severity until the beginning of November, 1924, when the patient was operated upon at the Brownsville and East New York Hospital, for cholelithiasis, but after a thorough search by two competent surgeons no gall bladder was found and a normal appendix was removed. Two weeks following operation pain in abdomen and cramps returned. Abdominal pain is not influenced by meals, but aggravated by coughing. The patient desires to urinate when attacks of pain come on. Cramplike nature of pain later disappeared, and there is no nausea or vomiting. Pains in back, especially right side posterior (December 12, 1924). Patient on admission also complained of nocturia three or four times.

Family History. This has no bearing on case.

Past History. The patient had measles, pneumonia and bronchitis, but had no operation, with the exception of the one five

weeks ago mentioned above. Menstrual and marital histories are essentially negative.

Physical Examination. The patient is undernourished. The mucous membranes are red. There are areas of pigmentation on the face and there are numerous irregular pigmented spots present all over the body, but no pigmentation of conjunctiva or mucous membrane of mouth. The teeth are in poor shape; bridgework is present, but no pyorrhea. The tongue is coated. The eyes react to light and accommodation; the pupils are equal. The mastoid is not tender. The ears and nose are negative. The thyroid is palpable. The epitrochlear, axillary and inguinal glands are not enlarged. The mammary glands are normal. The heart, with the exception of a moderate tachycardia, is negative. The lungs are negative. Tenderness is present at right trapezius, subscapular and right lumbar region. Right Murphy sign is positive. The abdomen is prominent—slight umbilical hernia (size of a quarter) is present; no dullness in flanks; no sign of fluid is present. Liver: Upper border in fourth space, lower border at crest of ilium; it is perfectly smooth; edge is sharply defined, hard and goes upward, until it is lost beneath the costal cartilage. Left side is not enlarged. It moves with respiration. The spleen is not enlarged. The kidneys are not tender nor palpable. The upper extremities are negative. The lower extremities—no involvement of bones, joints or muscles. No Babinski is present and all reflexes are normal.

The patient was in the hospital for three and a half weeks with normal temperature and pulse varying from 74 to 86 and respirations varying from 22 to 24. The systolic pressure averaged 130 and the diastolic averaged 80.

Laboratory Examinations. Numerous urine examinations were made and sugar was found varying from 1.1 to 5 per cent, with a daily output of 5.5 to 58 gm.; the daily output varied from 1200 to 2000 cc. Acetone and diacetic acid were also present. A few pus cells were found. After the nineteenth day from date of admission numerous examinations showed absolutely negative urine.

The blood showed the following:

BLOOD.

	Nov. 8, 1924.	Nov. 11, 1924.	Dec. 13, 1924.	Dec. 15, 1924.	Jan. 3, 1925.
Red blood cells	4,000,000		
Hemoglobin	75%		
Color index	1.0		
Coagulation time	6 minutes		
White blood cells . . .	15,600	13,200	13,800	14,400	10,200
Polymorphonuclears . .	78%	79%	76%	74%	38%
Eosinophils	1%	0	0	...	0
Lymphocytes	18%	19%	24%	26%	49%
Macrocytes and transi- tionals	3%	2%	0	...	12%
Mastocytes	0	0	0	...	1

The blood culture of December 18 proved sterile. The Wassermann test of the blood was negative. Blood chemistry: December 8: Blood sugar, 250 mg. per 100 cc. December 13: Blood sugar, 300 mg. per 100 cc.; urea nitrogen, 12 mg. December 16: Blood sugar, 20 mg. per 100 cc.; urea nitrogen, 16 mg; CO_2 , 46; creatinin, 1.2 mg. Gastric contents, 50 cc.: December 13: Total acidity, 30; free HCl, 16; no lactic acid; microscopically, starch granules and no blood. The feces showed, on examination of five different stools, no parasites, no blood, normal color, consistency and odor, with somewhat increased amount of fat. The Schmidt test for pancreatic function was positive.

January 3, 1925: A perinephritic puncture was done, and only a little blood was obtained, which on cytologic and bacteriologic examinations proved negative.

The Lyon-Meltzer test of December 18, 1924, showed the typical three-colored specimen: (a) 10 cc. of a golden yellow, (b) 50 cc. of dark green with much mucus and (c) a few cubic centimeters of a light yellowish fluid. This fluid obtained through the duodenal tube gave chemically all the tests for bile, showed a few red blood cells and leukocytes and a moderate number of bile-stained epithelial cells. No crystals were found. All sorts of contaminating bacteria were present.

Cystoscopic Examination (Dr. Goldfader). This showed bladder and ureter orifices normal; bladder urine clear. Roentgen ray catheters, 6F., inserted into each kidney pelvis without obstruction. Phthalein intramuscularly appears from each kidney in seven minutes. Specimens of urine from each kidney clear. Pyelogram and ureterogram of right kidney pelvis and ureter, with 10 cc. of 15 per cent sodium iodid for pelvis, 4.5 cc. of same for ureter and 2 cc. of 25 per cent argyrol into left kidney pelvis.

The urine obtained by cystoscope shows: Right kidney: Numerous red blood cells, occasional white blood cells and few cuboidal epithelial cells. Left kidney: Few amorphous urates and occasional red blood cells. Bladder: Numerous red blood cells (about 10 per high-power field). Cultures of 3 different specimens were sterile.

Roentgen Ray Examination (Dr. Strahl). The pyelogram shows no evidence of urinary calculi. The opaque catheters can be seen in the pelvis of both kidneys. Pyelogram is fairly good size. The ureterogram shows a slight dilatation at the juncture of the lower middle third and intermittent contractions at the lower one-third.

The fluoroscopic examination does not reveal any displacement of the right diaphragm or the presence of any intrathoracic fluid. The Roentgen ray picture shows an universal haziness in the abdominal cavity, more marked on the right side and suggesting disease in the right hypochondriac region.

Roentgen ray of the gastro-intestinal system shows the stomach

is not ptosed. Very active peristalsis, prepyloric filling defect. This filling defect is due to adhesions between the stomach and liver. Six-hour examination shows no gastric residue; the meal is in the terminal ileum; twenty-four-hour examination shows the meal in the large bowel; forty-eight-hour examination shows meal also in large bowel. Diagnosis: Intraabdominal adhesions. Gastrointestinal tract is negative.

The patient was given intravenously 5.5 gm. of tetrabromophthalein. She had a severe reaction, consisting of intense headache, chill, palpitation, vomiting and prostration. Cholecystogram revealed no gall bladder shadow.

REPORT OF BROWNSVILLE AND EAST NEW YORK HOSPITAL. (A personal conversation with the surgeons who operated upon this patient.) After exposure of the gastrohepatic omentum, and a most thorough search for the gall bladder, it proved to be congenitally absent. The common and hepatic ducts could be plainly traced, but there was no sign of the cystic duct. The walls of the duct were smooth and showed no knobs, thickening or dilatation. A large Riedel lobe of the lower liver was found. After a most thorough search of the entire abdomen, with negative results, a normal appendix and a piece of liver tissue were removed for pathologic examination. The liver showed microscopically fatty infiltration of liver cells with swelling of endothelium of bile ducts.

Urine Examinations. (Six examinations, before and after operation.) No sugar was found at any examination, and the urine was normal in every respect.

Blood Counts. On two occasions the blood showed: (1) Leukocytes, 9000; polymorphonuclears, 84; lymphocytes, 16. (2) Leukocytes, 8000; polymorphonuclears, 79; lymphocytes, 21.

Final Diagnosis. Riedel's lobe of liver; choleduodenitis; pancreatitis; diabetes.

Discussion. This patient, with a congenitally absent gall bladder, and having a Riedel lobe of liver, evidently had an infection which started in the common bile duct and ascended into the biliary ducts and ultimately involved the liver cells, as shown on microscopic pathology of the piece of liver removed at operation. This pathology explains the subjective and objective symptoms presented by the patient which led the surgeon to perform a gall bladder operation. The infection then traveled down the duct of Wirsung and involved the pancreas, particularly the islands of Langerhans, which gave rise to the symptoms of a rather severe diabetes. It is interesting to note how the biliary and diabetic symptoms completely disappears with the subsidence of the infection. The patient is perfectly well today on a regular diet.

I wonder what percentage of diabetes is due to an infection starting in the common bile duct and involving the pancreas secondarily by means of the duct of Wirsung or by the circulation! Whether,

in diabetes we would get better results if we paid more attention to the eradication of biliary infection, as was done in this case, by means of nonsurgical drainage, autogenous vaccines and so forth. I believe that the severe backache which made us suspect a perinephritic abscess, was really due to involvement of the pancreas.

Although no intraabdominal adhesions were present at the time of operation, they were quite marked shortly afterward, as evidenced roentgenographically. It is surprising how quickly and extensively these adhesions will form after prolonged intravisceral manipulations.

The pain and tenderness in the right lumbar region was so marked that in consultation with the genitourinary surgeons they favored the diagnosis of a kidney lesion, especially a perinephritic abscess. A complete urine examination cystoscopy, pyelography and a perirenal aspiration excluded any renal disturbance and saved the patient a useless operation. In a similar manner a right subdiaphragmatic abscess, which at one time was considered as a strong diagnostic possibility, on account of the severe pain and tenderness in that region, was excluded by aspiration, Roentgen ray pictures and especially fluoroscopy. This observation certainly lends additional confidence in the value of the employment of scientific investigation before operation to save the patients needless surgery.

There are many cases of congenitally absent gall bladder reported in the literature, and more cases are reported where the gall bladder is intrahepatic. L. C. Knox has encountered 2 cases of congenitally absent gall bladder in 2000 autopsies. These conditions are certainly not incompatible with life or even good health. These patients, however, are not infrequently susceptible to biliary disease and are often operated upon for cholecystitis or cholelithiasis, as was our patient. The question might be raised whether this patient did not have an intrahepatic gall bladder. Before cholecystography only an autopsy could have given a positive answer. But now we know that the live shadow cannot obliterate the shadow of the gall bladder filled with bile and tetraiodobromphenolphthalein. With the usual technique employed in cholecystography, the gall bladder shadow is revealed in spite of the fact that it is covered by the thickness of the whole liver, for the gall bladder lies not in front of the liver, but behind it. If the gall bladder were situated intrahepatically only part of this liver thickness would be in front of the gall bladder, and since the shadow of the whole liver thickness fails to obliterate the gall bladder, the shadow of only a part of the liver thickness would certainly not obliterate it.

Summary. This is the first reported case with a congenitally absent gall bladder on which cholecystography and the Lyon-Meltzer test were performed.

While most observers believe that the dark (B) bile comes from the gall bladder, there are some who doubt this. Observations

made on cholecystectomized man and animals do not approach the normal physiology of these biliary passages and therefore are not conclusive.

Here we have congenital absence of the gall bladder, and yet the patient presents, on the duodenal injection of magnesium sulphate, the three typical specimens of bile, including the dark (B) bile, which is supposed to come from the gall bladder.

There is only one conclusion to draw from this, and that is that the B specimen does not always come from the gall bladder, if it ever does.

A FINGER PUNCTURE METHOD FOR THE BLOOD SEDIMENTATION TEST.

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PHILADELPHIA.

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Not long after the blood sedimentation test was shown to have clinical value, attempts were made to perfect a technique requiring a small quantity of blood so that venipuncture would not be necessary. This is in the direction of simplicity and is highly desirable, for venipuncture at best is not without possible danger. In stout individuals with hidden and inaccessible veins and in children, some procedure not requiring venipuncture is a necessity, if this test is to be of universal application.

I wish to present a technique which utilizes the graphic principle of presentation (Cutler¹), but in which venipuncture is not essential. I call this technique the Pipette or Finger Puncture Method for the Graphic Presentation of the Blood Sedimentation Test in contrast to the Tube Method for the Graphic Presentation of the Blood Sedimentation Test in which venipuncture is essential. In the former a specially designed pipette is the all-essential apparatus, while in the latter it is a specially designed tube.

The details of the pipette method are as follows:

Apparatus Required. 1. A pipette, 2.5 mm. internal diameter with the stem graduated in 50 mm. divisions. The capacity of the graduated portion of the pipette is less than 0.3 cc., a quantity of blood easily obtained by puncture of the finger tip.

2. A metal spring attachment (Van Allen) for closing the bottom of the pipette after it is filled with blood.

3. A rack for holding sedimentation pipettes.

4. Small storage tubes, of about 1 cc. capacity in which the blood is collected and kept until ready for making observations.

5. Small rack for holding storage tubes.
6. A sharp lancet.
7. Sedimentation charts for recording observations.*

Procedure. 1. Select one of the fingers of the hand and carefully cleanse the distal phalanx with an alcohol sponge, rubbing briskly to induce hyperemia. It is sometimes of service to immerse the finger in hot water for a few minutes, especially in anemic individuals or where the skin is thicker than usual.

2. Puncture distal phalanx on its palmar surface and toward either side. This insures an easier flow of blood.

3. Collect blood in storage tube until about half filled (0.5 cc.). The storage tube which must be clean and dry is first filled with 3 per cent sodium citrate solution and its contents emptied. The quantity of citrate solution clinging to the walls of the tube is sufficient to prevent clotting of blood. From time to time the finger tip and the rim of the storage tube should be wiped with the citrate

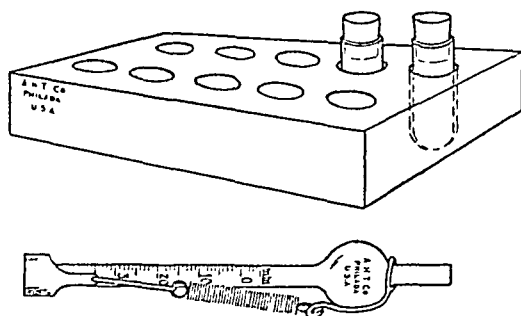


FIG. 1.—Storage tubes and rack. Sedimentation pipette with spring-sealing device (Van Allen) attached.

solution to remove possible clotted particles, and the tube shaken, as a further safeguard to prevent clotting. This is important. If clotting occurs the test must be repeated. In general the less the time consumed in obtaining the quantity of blood desired and the greater the ease with which the blood is obtained, the less the likelihood of the blood clotting and also the more accurate the result. I have not been able to obtain 0.5 cc. of blood from puncture of the finger tip without resorting to subsequent squeezing of the finger. Although there are objections to this procedure, for all practical purposes, as is evident from the results in the table and also in Fig. 3, if squeezing is done gently and systematically, dependable results will be obtained.

4. If samples of blood are to be obtained from several patients, place the storage tube in its rack and pay no more attention to it,

* These may be obtained from Charles M. Berkemeyer, Sellersville, Pa. The apparatus may be obtained from Arthur H. Thomas Company, Philadelphia, Pa.

until all the samples have been obtained. Cork each storage tube with a paraffin-coated cork to safeguard against accident.

5. When ready to make readings, (several hours may elapse with safety, after taking the samples of blood), shake each storage tube gently but thoroughly to insure uniform distribution of blood cells, for in many instances marked sedimentation may occur by the time one is ready to make readings.

6. Draw blood into the sedimentation pipette up to the zero graduation and attach spring cap to bottom of pipette. Here again certain details will prove of value. Draw the blood into the pipette by means of mouth suction on the rubber tube until the stem is filled with a *solid* column of blood, then holding the pipette in a horizontal position, remove the rubber tube and with pressure of the finger tip on the opening of the pipette, reduce the column of blood until the top is exactly at the zero mark.

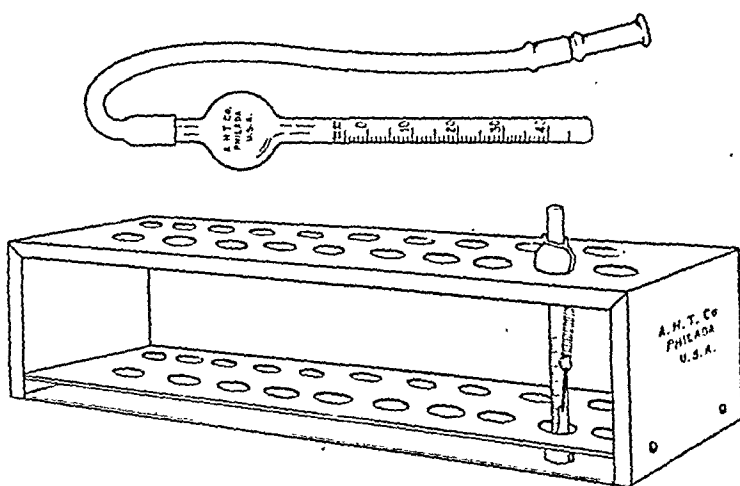


Fig. 2.—Sedimentation pipette and rack. The latter is constructed to provide complete visibility of each pipette during sedimentation.

7. Place the pipette in the sedimentation rack and determine the change in velocity by observing the position of the upper level of the sedimenting column of red blood cells every five minutes for one hour. These observations are recorded on the sedimentation charts, on which the horizontal lines represent the divisions on the stem of the pipette and the vertical lines the intervals of time. In this way a graph is traced which shows the position of the sedimenting column of red blood cells at any period of time during the first hour (see Fig. 3). The value of the sedimentation test is determined according to the path traversed by the red blood cells and depends upon the nature of the graph, sedimentation index and sedimentation time. All this has been fully described in a previous communication and reference should be made to that paper for clearer understanding. The purpose at present is simply to describe a new technique, not requiring venipuncture.

THE BLOOD SEDIMENTATION TEST IN PULMONARY TUBERCULOSIS.

Comparative Results of Tube and Pipette Methods, Both Tests Made Simultaneously upon Each Patient. Figures in First Line Opposite Case Number are for Tube Method, Serving as a Control, in Second Line for Pipette Method.

Case No.	Graph.				Sedimentation index, mm.	Sedimentation time, minutes.	Case No.	Graph.				Sedimentation index, mm.	Sedimentation time, minutes.
	Horizontal line.	Diagonal line.	Diagonal curve.	Vertical curve.				Horizontal line.	Diagonal line.	Diagonal curve.	Vertical curve.		
1 . . .	$\frac{+}{+}$	$\frac{1}{2}$		22	$\frac{+}{+}$	$\frac{10}{10.5}$	
2 . . .	$\frac{+}{+}$	$\frac{2}{2.5}$		23	$\frac{+}{+}$	$\frac{11}{10}$	
3 . . .	$\frac{+}{+}$	$\frac{2}{2.5}$		24	$\frac{+}{+}$	$\frac{12}{12}$	
4 . . .	$\frac{+}{+}$	$\frac{2.5}{3}$		25	$\frac{+}{+}$	$\frac{13}{13}$	
5 . . .	$\frac{+}{+}$	$\frac{2.5}{2.5}$		26	$\frac{+}{+}$	$\frac{10}{13}$	
6 . . .	$\frac{+}{+}$	$\frac{3}{5.5}$		27	$\frac{+}{+}$	$\frac{13}{14}$	
7 . . .	$\frac{+}{+}$	$\frac{3}{1.5}$		28	$\frac{+}{+}$	$\frac{14.5}{16.5}$	
8 . . .	$\frac{+}{+}$	$\frac{3}{3}$		29	$\frac{+}{+}$	$\frac{15}{14}$	
9 . . .	$\frac{+}{+}$	$\frac{4.5}{4}$		30	$\frac{+}{+}$	$\frac{16}{12}$	

10 . . .	$\frac{+}{+}$					31	$\frac{+}{+}$	$\frac{16}{15}$
11 . . .	$\frac{+}{+}$	$\frac{5.5}{5}$	32	$\frac{+}{+}$	$\frac{16}{16}$
12 . . .	$\frac{+}{+}$	$\frac{3.5}{5}$	33	$\frac{+}{+}$	$\frac{16}{15}$
13 . . .	$\frac{+}{+}$	$\frac{5}{5}$	34	$\frac{+}{+}$	$\frac{21}{19}$
14 . . .	$\frac{+}{+}$	$\frac{5.5}{2}$	35	$\frac{+}{+}$	$\frac{21}{17}$
15 . . .	$\frac{+}{+}$	$\frac{6}{5.5}$	36	$\frac{+}{+}$	$\frac{21.5}{20.5}$
16 . . .	$\frac{+}{+}$	$\frac{6.5}{9.5}$	37	$\frac{+}{+}$	$\frac{21.5}{20.5}$
17 . . .	$\frac{+}{+}$	$\frac{8}{8}$	38	$\frac{+}{+}$	$\frac{22}{22}$
18 . . .	$\frac{+}{+}$	$\frac{8}{6}$	39	$\frac{+}{+}$	$\frac{22}{23}$
19 . . .	$\frac{+}{+}$	$\frac{8}{10}$	40	$\frac{+}{+}$	$\frac{25}{25}$
20 . . .	$\frac{+}{+}$	$\frac{10}{9.5}$	41	$\frac{+}{+}$	$\frac{25}{25}$
21 . . .	$\frac{+}{+}$	$\frac{8}{13}$	42	$\frac{+}{+}$	$\frac{24.5}{22}$

BLOOD SEDIMENTATION TEST IN PULMONARY TUBERCULOSIS—(Continued)

Comparative Results of Tube and Pipette Methods, Both Tests Made Simultaneously upon Each Patient. Figures in First Line Opposite Case Number are for Tube Method, Serving as a Control, in Second Line for Pipette Method.

Case No.	Graph.				Case No.	Graph.				Sedimentation index, mm.	Sedimentation time, minutes.
	Horizontal line.	Diagonal line.	Diagonal curve.	Vertical curve.		Horizontal line.	Diagonal line.	Diagonal curve.	Vertical curve.		
43	+ —	+	53	+ —	+	21.5 — 20.5	45 — 50
44	+ —	+	54	+ —	+	23 — 23	45 — 50
45	+ —	+	55	+ —	+	25 — 26	40 — 40
46	+ —	+	56	+ —	+	28 — 30	45 — 40
47	+ —	+	57	+ —	+	25 — 26	40 — 40
48	+ —	+	58	+ —	+	28.5 — 29	40 — 40
49	+ —	+	59	+ —	+	29.5 — 31	40 — 45
50	+ —	+	60	+ —	+	29.5 — 29	35 — 35
51	+ —	+	61	+ —	+	26 — 25	35 — 30
52	+ —	+	62	+ —	+	30 — 30	30 — 25

If one compares the pipette or finger puncture method with the tube or venipuncture method it becomes evident that the pipette method is the tube method on a smaller scale, requiring a quantity of blood which can be obtained by puncture of the finger tip and that that is the only essential difference. The manner of recording and interpreting the results is exactly the same.

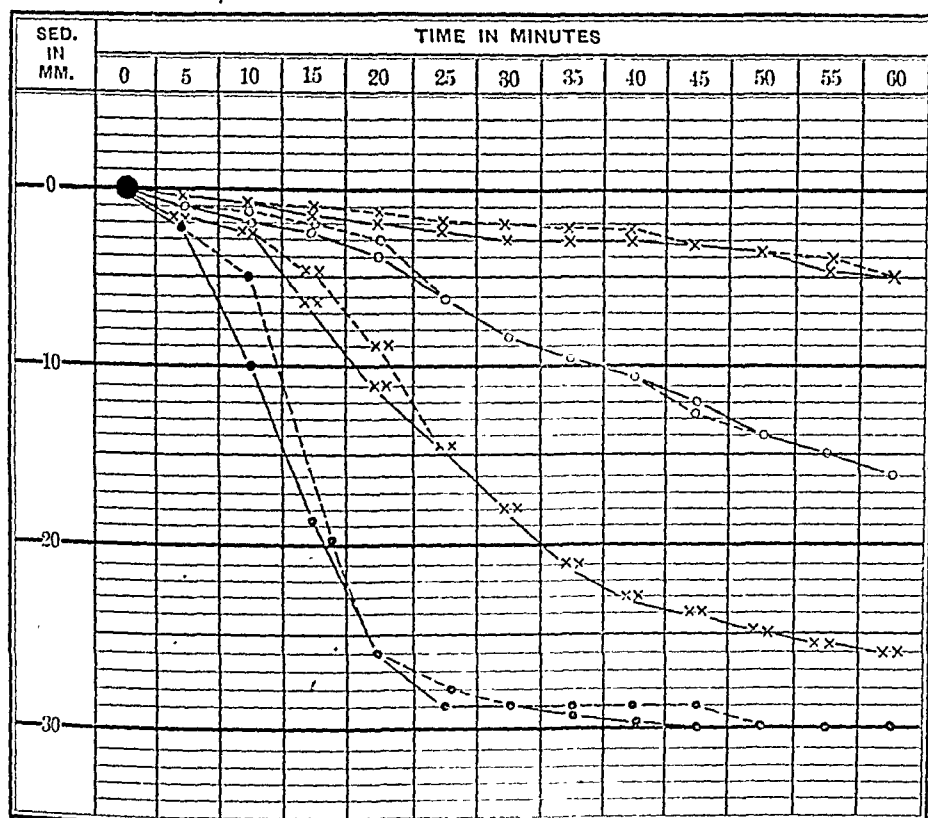


FIG. 3.—Comparison of graphs as obtained with pipette and tube methods.

- - x - - x - - } Horizontal line (clinically healthy individual).
 — x — x — }
 - - o - - o - - } Diagonal line (clinically quiescent tuberculosis).
 — o — o — }
 - - xx - - xx - - } Diagonal curve (clinically slightly active tuberculosis).
 — xx — xx — }
 - - . - - . - - } Vertical curve (clinically markedly active tuberculosis).
 — . — . — }
 - - - - - - - - - Graph obtained with pipette method, requiring puncture of finger tip.
 ————— Graph obtained with tube method, requiring puncture of vein.

The table on pp. 690–692 shows the comparative results obtained by the tube method in which venipuncture is essential and by the pipette method in which venipuncture is not employed, the blood being obtained by puncture of the finger tip. Both tests were made

simultaneously upon each patient, the tube method serving as a control in each instance. All patients studied were afflicted with pulmonary tuberculosis. It will be noticed that the pipette method parallels the tube method very closely and that the differences that occur here and there are of minor importance and do not interfere with a practical interpretation of the result. The character of the graph which is the all essential feature of the graphic method is the same in both.

Summary. A new technique is described for performing the blood sedimentation test, requiring a quantity of blood easily obtained by puncture of the finger tip, thus doing away with the necessity of venipuncture. This technique utilizes the graphic method of presentation developed by the author and described in detail in a previous paper.

NOTE.—I wish to express my thanks to Dr. Harry J. White for his valuable assistance.

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THE TRANSMISSION OF PATHOLOGIC SIGNS FROM A DISEASED TO A HEALTHY HEMITHORAX.*

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THE transmission of pathologic signs from a diseased to a healthy lung is a well-known phenomenon, but the mechanism responsible for it is variable and in need of investigation. The mode of transmission may be extrapulmonic and intrapulmonic, or may be a combination of both. The extrapulmonic transmission may be conducted through the bony thoracic structures, the pleural membranes, pathologic products of the pleuræ, as adhesions attached to the chest wall, and effusions. In this category may also be included pneumothorax. The intrapulmonic transmission is conducted through the lower part of the trachea, the bronchi, and both lungs.

A. The Extrapulmonic Mechanism. 1. The tone of a vibrating tuning fork, applied to the teeth, can be heard over the skull, along the entire vertebral column, and even over both elbows of the examined individual. The thoracic bony structures have a distinct

* From the Tuberculosis Division of the Montefiore Hospital for Chronic Diseases and Bedford Hills Sanatorium.

conductive power. Sounds emanating at one point of the chest can be conveyed along the bony framework to another part. (Turban¹ and Barach²). The following observation may be cited as an example of the transmission of pathologic signs by means of the spinal column and the ribs toward the healthy side.

Case Reports.—**CASE I.**—(No. 8361.) The patient had undergone a thoracoplasty on the right side. The partially collapsed lung contains a tuberculous cavernous lesion and emits bronchocavernous breath sounds with an amphoric quality. In addition there are loud pleuritic creaks synchronous with the phases of breathing. The left lung presents no evidence of clinical activity and its roentgenogram is negative. The mediastinal shadow shows marked displacement to the right. However, very loud bronchocavernous breathing, almost amphoric in character, is heard over the vertebral column at the level of the fifth to the eighth vertebræ, and over the left lung posteriorly, beginning at the fifth costal interspace down to the eighth. Over the left supraspinous fossa there are audible dry crackles of a pleuritic character, not synchronous with the breath sounds. On a subsequent examination, two months later, the amphoric quality of the breathing was still present over the collapsed lung and over the healthy side. The pleuritic sounds had disappeared from both sides.

Due to the thoracoplasty, the collapsed lung on the right side was in direct contact with the spinal column. As a consequence, the bronchocavernous breath sounds emanating from the cavity in the right lung were transmitted by conduction to the vertebral column, and from here to the left transverse processes of the vertebræ and the left ribs. Hence, the pathologic breath sounds were heard over the vertebral column and the left side. In addition the bronchocavernous breathing was probably also transmitted through the intrapulmonic route—by means of the trachea and bronchi. As to the pleuritic creaks, the close mechanical relationship which exists between the costal pleura and the ribs suggests that the bony thoracic framework may have transmitted them from the diseased right, to the normal left, side.

2. In patients with pneumothorax in which a flaccid mediastinum and a collapsed lung yield to the pressure of the insufflated air, pathologic signs may be audible on the untreated hemithorax. The collapsed lung, being displaced beyond the midline of the sternum or the spinal column, is thus enabled to convey signs to the sound side.

CASE II.—(No. 8345.) The patient was receiving gas insufflations every two weeks into the left pleural space. Physical examination showed: Right lung: No discernible abnormalities. Left lung: Hyperresonance anteriorly and posteriorly; absent breathing anteriorly and very feeble breathing posteriorly. Moist râles posteriorly extending from the hilum region downward and toward the axillary line. No cardiac displacement. Roentgenogram: Right, normal lung shadow; left, partially collapsed lung; apex and extreme base are adherent to the chest wall. Heart outline normal in size and position.

After the last insufflation, the physical examination revealed dextrocardia. In addition, there appeared a few moist râles near the right nipple and very many moist râles in the right intrascapular region. These râles were more intense over the spinal column, and became still louder when traced over the left hilum.

Fluoroscopy: The nonfixed portion of the left lung deviates together with the insufflated pleural space into the right hemithorax. There are pendulumlike oscillations of the entire mediastinum during the phases of breathing; on inspiration the right lung expands and pushes the mediastinum toward the left; on expiration the right lung contracts and simultaneously the left lung and the mediastinum move toward the right. The "to-and-fro" movement of the heart is especially marked, ranging from complete dextrocardia during expiration to almost normal sinistocardia during inspiration.

One month later, after some of the insufflated air had been absorbed and the left lung had ceased to protrude into the untreated hemithorax, no râles could be elicited over the right lung.

Analyzing the clinical data, it is obvious that the moist râles which appeared over the right hemithorax after the last refill were due to the extreme displacement of the partially collapsed left lung and the mediastinum toward the right. The râles were thus directly conveyed from the left lung through the spinal column which acted as a conductor and through the right chest wall, posteriorly and anteriorly.

B. The Intrapulmonic Mechanism. If a tuning fork be set into vibration, and the prongs be inserted into the open mouth, the tone produced will not be of sufficient intensity to be transmitted through the thoracic structures to the chest wall. However, intense pulmonary râles are known to be reverberated in the trachea and heard orally. We may assume that pathologic sounds of sufficient intensity, originating in a diseased lung, will be conveyed by the trachea and bronchi to the opposite healthy side. Considering that most of the pathologic sounds produced in the chest are not sufficiently intense to be transmitted by the intrapulmonic route, the latter will assume a minor, and even insignificant rôle beside the more powerful conductive mechanism of the bony framework.

CASE III.—(No. 8238.) The patient shows an unusual improvement after a very acute and extensive unilateral caseous pneumonia. The left upper lobe is destroyed, leaving a cavity. The pleura over the left lung is thickened and the heart is drawn to the left by adhesions. There are constant râles of a bubbling character over this lung. The roentgenogram of the right lung is negative. The percussion sound over the right lung is normal, and the breath sounds appear on auscultation only a trifle sharper than normal. Large, moist râles are heard over the right upper lobe, however, both anteriorly and posteriorly, which vary in their intensity; at times they are altogether absent.

CASE IV.—(No. 7761.) There is evidence of a large cavity in the left lung. The mediastinal structures are drawn to the left. Roentgenography of the right side shows only a marked accentuation of the root markings. There is cavernous breathing over the left lung. Distant cavernous breath-

ing is also audible over the right upper lobe, posteriorly and anteriorly. This sign on the healthy side was occasionally absent.

Review of the Literature. The first reported pathologic sign transmitted from a diseased to a healthy lung is bronchial breathing in croupous pneumonia. Fenger,³ in 1856, made the observation that in many patients with croupous pneumonia sharp bronchial breathing may be heard over the healthy side. The absence of consolidation on this side was checked up by postmortem examination. Sahli⁴ writes: "In pneumonia, bronchial breathing is heard not only over the consolidated area, but also over the opposite healthy side in the neighborhood of the spinal column." Skoda⁵ emphasized the resonating power of the bronchial structures made rigid through consolidation. Thus it becomes plausible that an immovable consolidated lung portion, while being in contact with the spinal column, may transmit the resonated or consonated bronchial breathing to the vertebræ and over the healthy lung by conduction.

The transmission of râles was detected in 1872 by Budde,⁶ Turban,¹ in 1899, likewise reports the transmission of moist râles to the healthy contralateral side; the transmission of sibilant and sonorous râles from one side of the thorax to the exact opposite point on the other hemithorax; and in pneumothorax very feeble "metallic breathing" on the healthy side. Turban attributes these findings to the conductive power of the bony parts of the thorax.

Korány,⁷ in 1897, noted in cases of pleural effusion a paravertebral triangular area of dullness on the healthy side near the base. Grocco,⁸ in 1902, and Rauchfuss⁹ made similar clinical observations. This paravertebral triangular area has since been designated by some as Grocco's triangle, by others as Rauchfuss' triangle. Baduel and Siciliano,¹⁰ in 1904, offered the following explanation for the causation of the dull percussion note obtained in Grocco's triangle. The fluid lying against and passing anteriorly over the bodies of the vertebræ acts as a mute in suppressing the vibrations of the spine. This deadening of the resonance is appreciable beyond the median line over the area corresponding to the transverse processes and the mesial part of the ribs. The displacement of the mediastinum is an additional factor in producing the dull percussion note and may even compress the nondiseased lung.

Analogous to Grocco's triangle, Carpi,^{11,12} in 1911, demonstrated in cases of pneumothorax a hyperphonetic zone on the contralateral side. This zone corresponds to the bulging of the pleural space at the posterior mediastinum produced by the tension of the gas. Carpi explains that the gas-distended space expands anteriorly over the midline of the spinal column so that with percussion of the spinal column and the adjacent chest wall, a resonant note is obtained, because this area will act as a resonator.

Carpi¹³ also established in 1912 that patients with artificial pneumothorax presented râles transmitted to the healthy contralateral side. He recommended for comparative auscultation in such cases the double stethoscope as originally proposed by von Muralt.¹⁴ He also claimed that the transmitted râles decreased as the air pressure was increased and disappeared completely when there was a complete collapse.

Heim and Jeanneret-Minkine¹⁵ compared the lung status before and after the induction of pneumothorax in order to identify râles transmitted from the diseased to the healthy side.

Solomon¹⁶ and Ameuille¹⁷ emphasize the fact that transmitted signs occur chiefly at the posterior aspect of the chest. Solomon believes that transmitted râles are never heard in the axillary space.

Lindblom¹⁸ reports 4 cases of pneumothorax in which râles were heard over the nontreated lung before insufflation; after air was introduced the râles diminished or disappeared. Solomon¹⁶ illustrated with 5 cases that the induction of pneumothorax obliterated the original source of the abnormal signs, and therewith the transmitted sounds disappeared. Thus pneumothorax can be used for diagnostic purposes.

Genevrier and André-Robin¹⁹ report, in 1922, an interesting case of right artificial pneumothorax in which the right apex was compressed against the spinal column; the râles from this apex were transmitted to the left apex. With a decrease in pressure the râles on the healthy side disappeared and became more audible on the diseased side.

Gendron,²⁰ in 1922, describes 1 case of partial pneumothorax with serofibrinous pleurisy in which on the healthy side the same pathologic signs were heard as over the diseased, even changed breath sounds and egophony. The sounds disappeared after refill. He claims that the fluid between the vertebral column and the noncollapsed portion of the lung conveyed the pathologic sounds. He mentions also the previously introduced theories for the transmission of pathologic signs; namely, that enlarged tracheobronchial lymph nodes and the vertebral column facilitate sound conduction.

Genevrier and Duval-Arnold²¹ suggest the following differential diagnosis for the transmission of abnormal signs: On auscultation, transmitted pathologic sounds will be synchronous with those on the diseased side. They will be qualitatively similar, but not absolutely identical. The localization will not be exactly symmetrical. The most frequent site of origin will be near the spinal column. The transmitted sounds will be heard most often in the paravertebral area or in the supraspinous and infraspinal fossæ. Vocal fremitus, which will be heard increased only over the diseased side, is a good diagnostic help, as well as unilateral dullness on percussion. Roentgenologic examination is important. (The author would like to add that such examination is not necessarily always conclu-

sive, since early lesions may be clinically detected before the roentgenogram demonstrates them.) Diagnostic pneumothorax is not reliable because, while the insufflation may interfere with the conduction of the râles to the surface of the thorax on the treated side, it would not hinder the direct transmission of these râles to the untreated side.

In addition, the paradoxical phenomenon can be mentioned that physical signs may be transmitted from a clinically healthy to a diseased hemithorax. Clark, Hadley, and Chaplin,²² in 1894, stated that in cases of fibroid disease of the lung and pleura, the resonant note usually elicited on the healthy side may be traced transgressing the midline, both along the sternum in front and the spine behind. Hamburger,²³ in 1906, detected in unilateral exudative pleurisy a resonant zone near the vertebral spine on the diseased side; and in the same year,²⁴ he also described a similar zone near the sternum on the diseased side in cases of pleurisy where the effusion extended anteriorly. He explains that during percussion of the affected hemithorax there are set up vibrations in the adjacent chest wall of the sound side, which, in turn, create a hyperresonant zone on the diseased side. Lillie²⁵ believes that the bulging of the emphysematous sound lung across the midline is the anatomic basis of the paravertebral resonant area on the diseased side. There is now under my observation a case (No. 8476) of unilateral pulmonary tuberculosis, presenting a fibroulcerative involvement of the entire left lung and thickening of the pleura. The roentgenogram shows a dense shadow occupying almost the entire left hemithorax; the mediastinum and heart are drawn to the left, and the right emphysematous lung protrudes over the midline. Percussion reveals an area of hyperresonance on the diseased side, adjacent to the vertebral column, which is especially pronounced at the base.

Summary. A. The following examples of transmission of pathologic signs have been noted:

1. Bronchocavernous breathing to the vertebral column and to the healthy lung posteriorly in a case of thoracoplasty.
2. Pleuritic creaks to the contralateral supraspinous fossa.
3. Moist râles to the anterior and posterior aspect of the opposite chest.
4. Cavernous breathing to the upper lobe of the healthy hemithorax, posteriorly and anteriorly.

B. An explanation for the mechanism of transmission is offered.

Conclusions. The transmission of pathologic signs from a diseased to a healthy lung is accomplished by means of two different mechanisms: (1) The extrapulmonic; (2) the intrapulmonic. They may act independently of each other, or in a combined manner.

While analyzing the pathologic states held responsible for the transmission of signs it must be borne in mind that secretions from a diseased lung may infrequently shift into the contralateral side,

creating temporary physical manifestations there. It must be remembered as well that certain nonpathologic conditions may be present in the nontuberculous side, such as muscle sounds, or definite pathologic changes, such as tumor, bronchiectases, etc., which may simulate transmitted signs.

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EARLY CRANIECTOMY AS A PREVENTIVE MEASURE IN OXYCEPHALY AND ALLIED CONDITIONS.

WITH SPECIAL REFERENCE TO THE PREVENTION OF BLINDNESS.

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PREMATURE synostosis of the cranial sutures, particularly of the coronal and sagittal, is a disorder which has extremely serious complications and sequelæ, notably, marked deformity of the face and head, increase of intracranial pressure and, in a very large proportion of cases, partial or complete loss of vision from optic atrophy. Operation for the condition has up to the present been performed only as a palliative measure after complications or sequelæ have developed and irreparable damage has occurred. For reasons to be discussed it is probable that the evil effects of synostosis are largely preventable by a suitable operation performed sufficiently early in life. Mehner,¹ in 1921, proposed "extirpation of the synostosed suture," but we find no record that his suggestion was ever carried out. In 1924 one of us,² unaware of Mehner's proposal, advocated the revival of the Lane-³Lannelongue⁴ operation of linear craniectomy or craniotomy, which had for many years fallen into disrepute because it had been mistakenly used in the treatment of anencephalic microcephaly and other incurable forms of idiocy.* It was pointed out that in oxycephaly and allied conditions there is no primary brain defect, but that the deformity arises from mechanical interference with the growth of the brain by a relatively inexpandable skull, and that increased intracranial pressure and loss of vision occur as late sequelæ. The removal of ample strips of calvarium, if done during the period of rapid growth, might logically be expected to permit approximately normal development of the skull and thus prevent the serious consequences mentioned.

We now wish to present the case report of a child operated upon in 1924, who has been under close observation during the ensuing two years.

CASE I.—Baby C, male, born on December 12, 1923, birth weight 7 pounds 8 ounces, was admitted, January 12, 1924.

* Jacobi (Med. Rec., 1894, 45, 609) said "If any cases be at all amenable to treatment by such an operation, they must be those of uncomplicated premature ossification of the sutures and fontanelles."

Family history: Father and mother are young and in good health. One previous pregnancy ended in abortion, cause not stated, December, 1922.

Birth was at full term, with head presentation; no instruments; no difficulty noted, but membranes are said to have ruptured five days before delivery. There was no asphyxia. Bottle feeding was begun at three days.

Present complaint: Feeding directions were desired.



FIG. 1.—May 6, 1924. Age, five months. There is slight asymmetry with prominence of the left temporal region; a rather wide interocular space; prominence of the forehead, marked backward and downward slope of the calvarial profile posterior to the bregma, prominence of the occiput, and marked bulging of the temporal veins on crying.

Physical examination: In other respects normal, the baby was found to have marked malformation of the skull. The frontal region was square and large, the anteroposterior diameter long. The parietal and occipital regions were flattened laterally and the occiput elongated, the whole posterior half of the calvarium giving the impression of being pinched in the transverse direction. The anterior fontanelle was triangular with the apex anteriorly, the angles continued with the metopic and coronal sutures which were wide open; the posterior border was almost a straight line, without a notch for the sagittal suture, which was apparently closed nearly to the posterior fontanelle and its line indicated by a bony ridge. There was no proptosis of the eyes. The temporal veins were prominent, especially on crying. No syndactylism or other malformation was present. Blood Wassermann test was negative.

Roentgenologic report: "The sagittal suture is ossified. Coronal, occipital and frontal sutures gaping."

Diagnosis: Premature synostosis of the sagittal suture; scaphocephaly.

By April 15, 1924, another examination showed several changes to have occurred. Definite asymmetry was now present. The right side of the forehead was more prominent than the left, the right parietal region more rounded and elevated than the left.



FIG. 2.—June 27, 1924. Age, six and a half months. Taken eight days after operation. The eyes show slight proptosis and the palpebral fissure is wide. The veins do not appear. The postbregmatic region is more rounded and elevated than before operation.

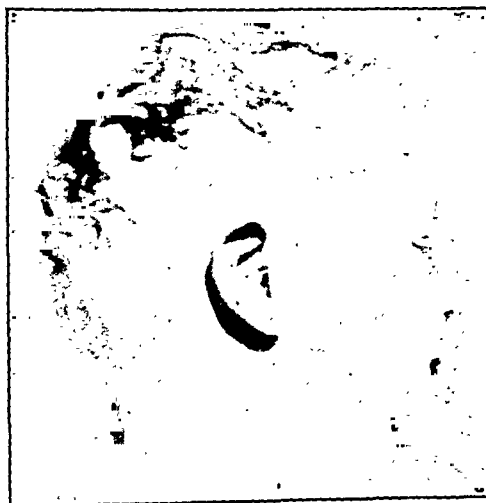


FIG. 3.—January 13, 1925. Age, thirteen months. The calvarial profile appears normal. The highest point of the skull is now at about the midparietal point instead of at the bregma, as before. The occiput is not prominent.

The forehead, as a whole, was more protuberant, the occiput less so. The fontanelle had greatly narrowed (about 0.6 by 3 cm.). The head was much broader in relation to its length than before. No proptosis was present and the eyegrounds were normal.

On June 17 the anterior fontanelle was practically closed. Bulg-

ing of the temporal regions and beginning proptosis were now present. The head was markedly brachycephalic. The temporal veins were very prominent. The fundi were normal.

Although in the roentgenogram the coronal sutures could be seen, the changes in the shape of the skull and the apparent closure of

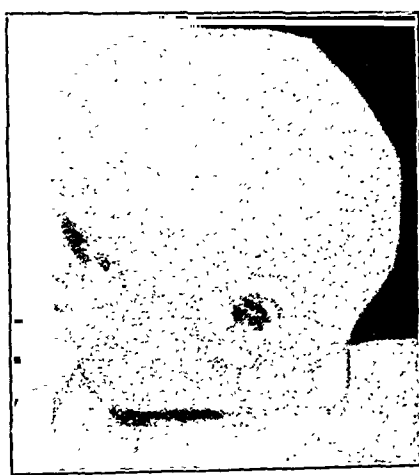
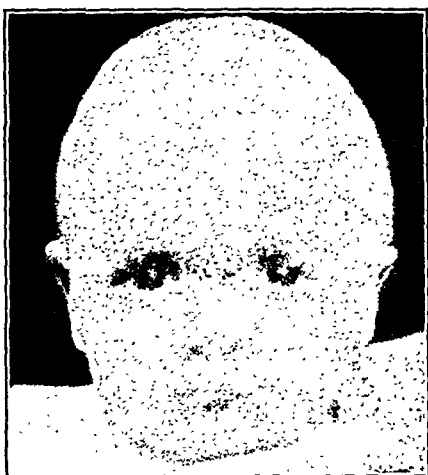


FIG. 4.—July 2, 1925. Age, eighteen and a half months. A slight bulge of the left temporal region is still discernible. The profile appears normal. The interocular distance appears to be relatively less than in Fig. 1.



FIG. 5.—November 29, 1926. Aged, three years. The slight bulging of the left temporal region is the only remaining deformity. The child does not habitually hold the mouth open.

the fontanelle strongly suggested that these sutures were closing, the left perhaps more than the right. It was evident that there was an increasing maladjustment of the brain and brain case and possibly beginning increased intracranial pressure. After full discussion with his mother, it was decided to perform a linear craniectomy, which was done on June 19, 1924. The notes of the operation follow:

Operation by E. B. T., June 19, 1924: Linear craniectomy, under ether anesthesia. A transverse scalp incision was made between points 2 cm. above each external auditory meatus. The scalp was dissected backward to expose the upper portion of the lamboidal suture, and forward to expose the coronal sutures. The lamboidal and left coronal sutures were open; the sagittal and right coronal were closed. There was an open metopic suture. Two channels were cut in the cranial bones; the first was to the right of the sagittal suture and extended from the coronal to the lamboidal suture; the second lay posterior to the coronals, and extended from one squamoparietal suture to the other. The channels were 1 cm. wide and included the overlying pericranium. A wick of rubber tissue was

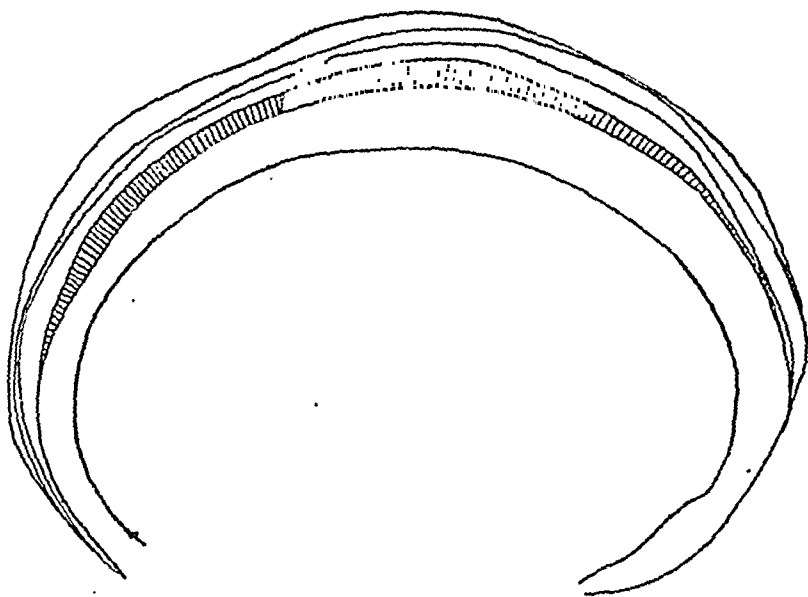


FIG. 6.—Superimposed tracings from the lateral roentgenograms of the skull dated January 14, June 18 (one day before operation), June 25 (six days after operation), August 12, October 21, 1924, and April 9, 1925. The shaded area represents the expansion of the skull occurring within the six days following operation.

passed through a stab wound over the posterior end of the sagittal craniectomy, and the scalp incision was closed with two layers of interrupted sutures.

Postoperative course: The drain and cutaneous sutures were removed on the third day. The wound healed cleanly. The child was dismissed from hospital on the seventh day.

Six days after the operation roentgenograms showed that the vertical diameter of the skull (sella to vertex) had increased about 4 mm.

By August 12 the proptosis had entirely disappeared, the forehead was less bulging and the temporal veins were less prominent. The anteroposterior craniectomy had widened to about 2.5 cm. at the new fontanelle, which pulsed and showed a normal crying impulse. The temporal bulging persisted, more on the left. Viewed from

above, the asymmetry was decidedly less marked. The mother was impressed with the child's improvement in appearance and behavior, stating that he appeared brighter, cried less and played more actively (indicating at least that the baby was making normal progress for his age). Tracings from the roentgenogram of this date shows growth of the skull in all directions, the brachycephaly being slightly more marked.

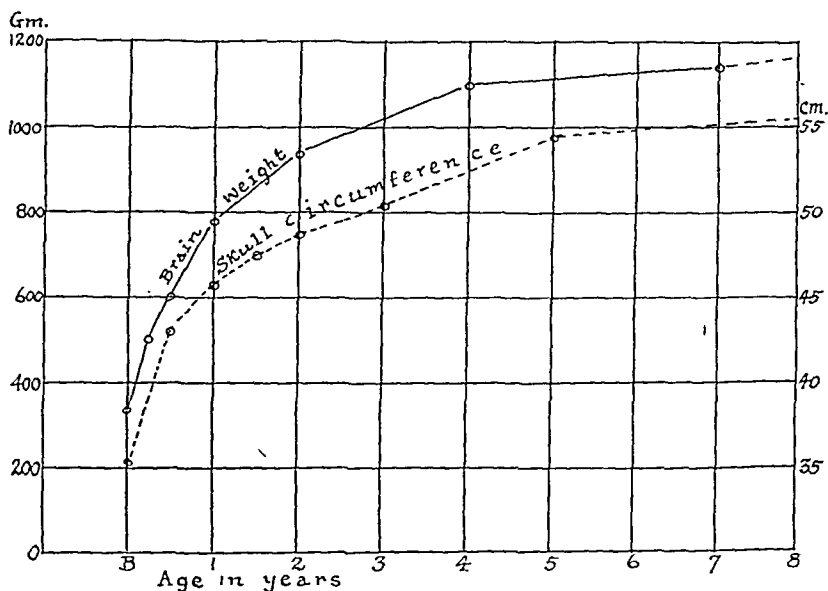


FIG. 7.—Graph showing the normal growth of skull and brain during early childhood.

By October 10, 1924, the artificial sutures were definitely filling in with new bone. The prominence of the forehead was less. The posterior portion of the skull had grown considerably, the anterior but little. No proptosis was present. The appearance was notably improved. The child was walking without support, could say a few words and had eight teeth.

By January 13, 1925 (age, thirteen months), the channels made in the skull had apparently closed. There was no striking change in the shape of the skull from that last noted.

By April 7, 1925, the head was apparently normal in shape and appearance. Mentally the child was "certainly normal," perhaps brighter than the average for his age. Plates at this time showed considerable growth of the skull to have taken place.

A more careful note on July 2, 1925, stated that slight bulging of the temporal fossæ and of the forehead could be detected and that the parietal dome was slightly flattened, but the appearance as a whole was not notably abnormal. The photographs bear out these statements. At nineteen months of age the child talked freely, forming short sentences, knew his alphabet and could count to ten.

Photographs and measurements in February, 1926, show a child of essentially normal appearance and development. On November 29, 1926, after the completion of our manuscript, the patient was again seen and photographed. He was then just under three years of age and two and a half years had elapsed since the operation. While a slight asymmetry of the head can be detected when his hair is flattened as it was for the photographs the configuration of face and skull is very nearly normal. His physical and mental progress continue to be excellent. No visual defects have developed.

Summary. This patient before operation showed a rapidly progressing deformity of the skull, due to synostosis of the sagittal suture, and later synostosis of one or both coronal sutures, with signs of beginning increase in intracranial pressure. The deformity, at first that of a simple scaphocephaly, had changed in the direction of oxycephaly. Following operation the shape and development of the head became approximately normal. The chief demonstrable benefit has been cosmetic. It is possible that blindness from optic atrophy has been avoided.

Comment. In this case it is probable that we have restored some, if not all, of the conditions necessary for the normal development of a skull which, already deformed by sutural synostosis, was likely to develop increasing deformity and widespread disturbance of the anatomic relationships, not only of the calvarium, but of the base, the orbit and the soft parts, possibly including the optic nerve. The results obtained then may be fairly regarded as of much more than simple cosmetic importance. In justification of our advocacy of preventive operation in similar cases and of linear craniectomy as the operation of choice, we wish to call attention to the frequency of visual impairment and to the pathologic conditions responsible for it.

Algyogyi⁵,⁶ in one place estimates the incidence of impaired vision at over one-third and in another at almost one-half of the cases of tower skull. Fifteen, or 71 per cent, of Mehner's¹ 21 cases showed it. Beyond doubt, many cases escape notice until they come to the ophthalmologist for loss of vision, and accurate figures must, therefore, be impossible to obtain. However, Fletcher⁷ in his careful review says of the vision in oxycephaly: "This is occasionally unimpaired, but in the vast majority of cases sight is very defective."

Sight is, as a rule, impaired quite early in life. Meltzer's⁸ tabulation of 20 cases illustrates this point:

	Deformity first noticed.	Blindness first noticed.
At birth	13	1
During first year	1
During second year	7	1
During third year	10
During fourth year	3
During fifth year	1
During sixth year	3

It is particularly worth noting here, too, that diagnosis is possible in the great majority of cases before vision has been lost.

Choice of operation for both preventive and palliative operation depends upon the underlying pathology and, unfortunately, much confusion has arisen from a long-standing difference of opinion as to whether the optic nerve disturbance has its origin in simple constriction by a narrowed optic foramen or in increased intracranial pressure. The first of these theories forms the basis for palliative canal widening operations, which have been performed a number of times. It is founded on 4 necropsies, 1 by Michel⁹ (1873), 1 by Ponfick¹⁰ (1886), 1 by Manz¹¹ (1887) and 1 by Behr¹² (1910). These have been so frequently referred to in support of the theory that we have examined 3 of the original reports for details. Michel's patient, a boy, aged fifteen years, blind since birth, showed optic nerves very narrow and flat, with the sheath filled and apparently distended with a peculiar granulation tissue. There was some evidence of syphilis. The narrowing and flattening of the nerve extended from the chiasm to the optic bulb; the diameter of both nerves within the sheath was the same without and within the foramen, while the horizontal diameter was 0.5 mm. and 0.3 mm. less within the foramen. In this case compression of the nerve obviously had occurred both within the foramen and in the intracranial cavity. The slight additional compression in the foramen may have been, and apparently was, due to an overgrowth of granulation tissue within the optic sheath rather than primarily to narrowness of the canal, about which no exact details are given. Ponfick's report has not been obtainable. Manz's necropsy was done hurriedly, and he states that no direct observation of the foramen was made; he did, however, note that all the foramina observed were widened and that the anatomy of the bones of the skull, especially at the base, was much distorted. Manz based his deduction that the foramen was narrowed on an observed constriction ("Einschnürung") of the nerve at its point of entrance into the foramen.

Behr, in a report to be cited presently, found a similar constriction, but gave it a different explanation. Dorfmann¹³ in a dried museum skull found a narrowing of the foramen and, in addition, noted a deep depression of the median portion of the anterior fossa, the cribriform plate deeply depressed, a very deep optic groove and other deformities. Weiss and Brugger,¹⁴ in 4 skulls, Vortisch,¹⁵ in 1, and Enslin,¹⁶ in 6, failed to find narrowing of the optic foramen. Larsen¹⁷ and Bedell¹⁸ in necropsies likewise failed to find it. White,¹⁹ in his recent roentgenologic measurements in patients with optic atrophy, found the optic foramina normal in 2 oxycephalics and definitely enlarged in 4. Both Dorfmann and Behr found the nerve flattened and elongated from the chiasm distally, thus presenting evidence of intracranial pressure or stretching. Behr found a remarkable displacement of the relations between the optic nerve,

foramen and internal carotid artery resulting in pressure on the nerve at the margin of the inner end of the foramen by the artery, which formed part of the internal wall of the foramen. The bony part of the foramen was not narrow. The nerve was flattened and so elongated and displaced that the chiasm rested on the dorsum sellæ.

The evidences of profound dislocation of the normal anatomic relationships at the base in tower skull are many, and cannot all be cited here. The cribriform plate has often been found deeply depressed, and in Larsen's case a hernia of the brain into the nose had occurred. The great wing of the sphenoid has usually been found directed transversely instead of obliquely, thus forming the posterior instead of the lateral wall of the orbit which was accordingly shortened and deformed and its axis changed. The vertical diameter of the orbit may be lessened by as much as 10 mm. (Friedenwald²⁰) by downward pressure from above. Dorfmann also noted an accompanying synostosis of the hard palate, causing a high and narrow palatal arch, with marked deviation of the nasal septum. The evidences of increase of intracranial pressure are usually clear and sometimes extreme. The convolutional markings are deep on the calvarium and on the superior walls of the orbit, the former giving a striking roentgenographic picture. The cranial fossæ are often deepened. The clinical symptoms and the appearance of choked disk in several cases seen early,^{7, 13} also testify to increased pressure.

In short, it is clear that the interference with skull development from synostosis, especially of the coronal and sagittal sutures, leads to a profound and widespread anatomic dislocation. The skull, unable to expand in all the normal directions, under the growth pressure of the brain is forced to expand at the remaining points of least resistance—the posterior and lateral portions of the calvarium, the cribriform plate, etc. If the compensatory deformities so produced are inadequate there results a progressive rise in the intracranial pressure. This is a gradual process and the pressure apparently does not reach the critical point at which damage to the optic nerve is produced until compensatory expansion has reached its limits. Clinically, this is not often before the third year. In some cases it may be that deformities of the body or wings of the sphenoid lead to narrowing of the optic foramen or to pressure on the nerve by a displaced carotid artery, but even here it seems likely that such changes are traceable to compensatory malformation of the bones of the cranial base from brain pressure. If this be true it forms an added argument for attempting correction before deformity is far advanced. From both views of the pathology, linear craniectomy sufficiently extensive to permit adequate expansion of the growing skull and brain seems to be a logical and justifiable means of prevention of further deformity and of eventual loss of eyesight.

Simple extirpation of the synostosed suture, as suggested by Mehner is probably not enough, and in our opinion a cruciform incision extending nearly the whole length of the coronals and from the bregma to the lambda should be performed unless the sagittal suture is wide open throughout its length. This opinion is based on the fact that when such an excision is made the skull at once expands, spreading the artificial suture and releasing the dura and brain from the tension existing at the time. This phenomenon is not noticeable until the excision has been made in both directions. Another reason is found in the fact that previously open coronal sutures may close prematurely and increase the disability. This occurred in our patient, both of whose coronals were wide open at the age of one month. Between that time and the age of six months, when he was operated upon, the head had rapidly changed from scaphocephalic to brachycephalic, and at operation one of the coronals was found to be closed. It seems clear from the cases reported in the literature and those we have seen that closure of the coronals is by far more serious, in respect to deformity and loss of vision, than that of any of the other sutures.

The operation should be performed as early as possible, before malformation has progressed too far and heightened pressure has begun to develop. The most promising period in our opinion is during the first six months; after the second year satisfactory results are hardly to be expected. As shown in the accompanying graph, growth of the skull and brain is very rapid during early infancy. The normal skull circumference during the first six months attains about 40 per cent of its postnatal growth, and during the first year more than one-half. During the first six months the brain increases in weight about 85 per cent and during the first year 135 per cent.²¹ After the first year growth of both skull and brain become progressively slower. The reason for the rapid development of compensatory deformities from synostosis during the first year is obvious, and it is equally obvious that if these and their sequelæ are to be prevented the earlier operation is done the better.

Diagnosis presents few difficulties. Characteristic deformities appear, as a rule, early in infancy and frequently at birth. A ridge along the closed suture can often be felt. The abnormally small head of anencephalic microcephaly is readily distinguished from the head distorted by synostosis, in which the decrease in one dimension is compensated for by increase in another. In the former symptoms of idiocy are early manifest; in the latter mental defects are, as a rule, absent, but if they occur at all they appear much later, usually in late childhood. Symptoms and signs of increased intracranial pressure are wanting in microcephaly. Roentgenograms are usually of value, but in infancy the sagittal is not always easily demonstrable through its whole extent, and a recently closed suture may continue to show as an ill-defined line of lessened density.

Conclusion. In conclusion, it should be said that while synostotic deformities are not very uncommon, they seldom constitute a presenting complaint. Parents, as a rule, do not seek medical advice for a peculiarity of appearance, best unremarked, in their children. If the diagnosis is to be made more often and earlier it devolves upon the physician, particularly the pediatrician and the obstetrician, in the routine of private or clinic practice, to focus his attention for a moment on the skull configuration of each infant and child he sees. Discovering one of these cases, he should realize that the chances of eventual blindness are extremely high, and that operative interference for restitution of normal skull development and for the conservation of vision may be undertaken with small risk.

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GENERAL PARESIS.

A CLINICO-PATHOLOGIC STUDY WITH ESPECIAL REFERENCE TO
THE SIGNIFICANCE OF THE SO-CALLED "TYPICAL"
LABORATORY FINDINGS.

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AMONG the various forms of mental disease there is none which may start in such a variety of ways and exhibit such a protean symptomatology as general paresis. It has been known for a long time that the initial symptoms of paresis are often similar to those of the psychoneuroses; the onset may also be with excitement, depression, or a paranoid trend. Recently Bunker¹ has reviewed the records of 74 paretics, interviewed their relatives, and found that some of them showed psychic abnormalities for at least four years before the mental breakdown occurred. Irritability, "nervousness," bradyphrenia and other common neuropsychiatric complaints were among some of the frequent early symptoms in Bunker's cases. How often is the significance of such symptoms overlooked!

It goes without saying, therefore, that long before the old conception of paresis, namely, delusions of grandeur and dementia, occurs, that there must be prodromal symptoms which may antedate the acute mental upset by years.

Paresis is such a common mental disease (making up, as it does, 20 per cent of those in mental hospitals) and may masquerade under such different guises that it should always be thought of in any psychiatric disturbance occurring between the ages of twenty-five and seventy years; furthermore, juvenile paresis is common enough in the psychoses of childhood.

From a diagnostic standpoint too much stress has been laid upon the grandiose form of paresis and too little upon the other and more common ways in which the disease asserts itself. Once general paralysis is in full bloom with changes in character, delusions of grandeur, physical signs and mental deterioration a tyro can, or at least should, make the diagnosis with facility. If we have in the form of laboratory examinations anything which will anticipate the almost irreparable brain damages which occur in paresis it would be a means of saving at least a few cases from mental catastrophies.

From the pathologic angle our conception of paresis is a syphilitic meningoencephalitis characterized by a fibrous thickening and infiltration of the meninges with round cells of the lymphocytic and plasma type, the infiltration being particularly limited to the deeper pial layers. In the cortex the findings are a breaking up of the architecture independent of the vascular supply, perivascular infiltration with cells identical with those of the pia, the occurrence of rod cells in great number, and new vessel formation. By means of the newer staining methods we can detect the increase of iron and enormous numbers of so-called Hortega and Cajal cells of the glial type. A certain percentage of cases, probably not over 15, have sclerosis of the posterior columns of the cord and the usual syphilitic meningitis, producing the clinical picture that is commonly called taboparesis. Remissions, either spontaneous or as a result of therapeutic measures, may bring about decided improvement in the pathologic picture.

Since Lange described the gold-sol reaction in 1912 a considerable literature has sprung up on the subject, and it has come to be an integral part of every complete spinal-fluid examination. The so-called paretic curve in itself does not mean paresis but may occur in a number of other conditions such as multiple sclerosis, neurosyphilis other than paresis, meningitis especially tuberculous, occasionally in cerebral tumors and at times in other conditions such as epidemic encephalitis; certainly a syphilitic curve frequently is found in the foregoing diseases. While the paretic curve is not pathognomonic of general paresis, the absence of it in the spinal fluid of a paretic, virgin from the therapeutic standpoint, is a rather rare occurrence. When the paretic curve is combined with other cerebrospinal fluid evidences of syphilis it is of great diagnostic importance. We refer of course to a positive Wassermann reaction with different amounts of the fluid, pleocytosis and an increase of globulin. If all the laboratory tests enumerated are positive and in addition a positive Wassermann reaction in the blood is found, are we justified in assuming that such a case is incipient general paralysis of the insane even in the absence of mental symptoms? If mental symptoms are present, is such a case always paresis or may the patient have neurosyphilis and a psychosis non-paretic in origin?

To answer these questions, at least in part, we have analyzed the records of cases which were correctly or incorrectly diagnosed general paresis, who died and whose brains were obtained and examined. In addition we reviewed the histories of 10 cases in which the diagnosis of paresis was made or was considered because of the laboratory tests, and later we examined the brains of the series.

We have divided the cases into the following groups:

1. Thirty-nine cases in which the diagnosis of paresis was made on the history, physical and mental examinations and laboratory

tests and the diagnoses were proved to be correct by microscopic studies.

2. Six cases with the so-called typical laboratory findings; the cases were proved by examination of the brains to be paresis but were diagnosed incorrectly.

3. Twelve cases diagnosed paresis, some of whom had paretic laboratory findings but on microscopic examination were found not to have general paralysis of the insane.

4. Ten cases in which the diagnosis of paresis was considered and in which the laboratory findings were suggestive but the cases were neither diagnosed paresis nor did they have paresis on microscopic study.

Group 1. Of the patients who fell under this heading, every one to a greater or less degree had laboratory findings indicative of paresis. However, as in any group of cases the clinical records of which are studied after death, many examinations were missing but the information available is well worth while summarizing. Of the 39 cases all but 3 had positive Wassermann reactions of the blood, giving a percentage of 92. Of the 3 cases who had negative blood Wassermans one had received a great deal of intravenous therapy. The spinal fluid Wassermann was not done in 1 case; in a second the fluid was anticomplementary; in all but 1 of the remainder it was 4+. The 1 case which showed a negative spinal fluid Wassermann was admitted to the Philadelphia General Hospital in coma, had status epilepticus and died in a few hours. Subsequent investigation of the woman's history showed that she had received intravenous therapy over a prolonged period. The colloidal-gold curve was paretic in type in every case except 1; this patient had had antisyphilitic treatment and the gold test in this case showed the syphilitic curve on two occasions, and one time gave no curve at all. The cerebral pathology, however, was typical of paresis. The cells in the spinal fluid were estimated in all but 4 cases and the average was 31, the count ranging from 1 to 400. The globulin was not estimated in 8 cases, in the remainder it was negative in 1 and increased in the others.

Group 2. While this series of cases is not large, a consideration of them is of great importance. It proves conclusively, at least to us, that mental symptoms when combined with the so-called typical laboratory findings of general paresis always make that diagnosis the most likely one and that the burden of proof is on the shoulders of him who says such a case is not one of general paresis. In fact he who persistently and stubbornly refuses to acknowledge the importance of such a combination is either a super-diagnostician or one whose audacity will constantly get him into trouble.

Group 3. This division consists of 12 cases which were diagnosed general paresis. Some of them had the laboratory findings extremely

suggestive of such a condition but pathologically none of them were general paralysis of the insane.

TABLE I. GROUP 2.—CASES OF PARESIS DIAGNOSED INCORRECTLY.

Clinical diagnosis.	Laboratory findings.						Pathologic diagnosis.
	Blood Wassermann.	Spinal Wassermann, cholesterin.	Spinal Wassermann, Noguchi.	Cells per cu. mm.	Globulin.	Colloidal-gold curve.	
Right cerebral hemorrhage and tabes . .	Not done	4+	4+	3	Not done	5555543511	Tabo-paresis
Amebic abscess of liver and tabes	Neg.	2+	Neg.	22	Trace	5555554310	Tabo-paresis
Syphilitic meningitis . .	4+	4+	4+	5	2+	5555555520	Paresis
Tabes	4+	4+	4+	0	Trace	5555432100	Paresis
Syphilitic meningomyelitis . .	4+	3+	3+	60	4+	5555543211	Paresis
Dementia præcox . .	4+	4+	4+	6	Neg.	5555543100	Paresis

Group 4. This group covers 10 cases in which the diagnosis of paresis was considered and in which the laboratory findings were suggestive but the cases were neither diagnosed paresis nor did they have paresis on microscopic study.

Comment. An analysis of the records which we have presented shows that the vast majority of cases of general paresis have strongly positive evidences of syphilis in the blood and spinal fluid, including the presence of the paretic gold curve. Cases of neurosyphilis other than general paresis, however, may show almost identical laboratory reactions. Sicard and Haguénau² believe that the favorable results in the treatment of general paresis reported by American and Austrian writers are due to the inclusion in their series of certain cases of cerebral syphilis. Our series of cases certainly bear out this fact. If one, in making the diagnosis of general paralysis of the insane, depends entirely upon the so-called paretic laboratory findings he will often be led astray; an incorrect belief in the infallacy of these tests, as a short cut to diagnosis, may be engendered by a feeling of uncertainty in one's diagnostic ability in the specialty of neuropsychiatry.

TABLE II. GROUP 3.—CASES DIAGNOSED PARESIS INCORRECTLY.

Sex.	Age.	Clinical summary.	Laboratory findings.						Pathologic diagnosis.
			Blood Wassermann.	Spinal Wassermann, cholesterin.	Spinal Wassermann, Noguelt.	Cells per cu. mm.	Globulin.	Colloidal-gold curve.	
F. . . .	57	Incontinence, dizziness, generalized twitchings; pupils fixed; perforated septum; reflexes increased; Jacksonian convulsions; euphoria; delusions of grandeur	4 +	4 +	4 +	4	None	3555554221 4444442211	Gumma left frontal lobe; softening, right frontal lobe; gumma, left parietal region
M. . . .	61	Attacks of temporary paralyses of lower extremities; incontinence of feces; alcoholic; pupils sluggish; reflexes increased; euphoric; grandiose	Neg.	Neg.	Neg.	2	Faint trace	0012211000	Arteriosclerosis with areas of softening
F. . . .	60	Sick two years, weakness of hands; low mentality; Jesus spoke to her; pupils rigid; loss of speech; coma	4 +	4 +	4 +	20	Trace	1123321000	Arteriosclerosis Thrombosis of superior longitudinal sinus
M. . . .	55	Right hemiplegia and aphasia	4 +	4 +	4 +	80	Trace	5555543100	Thrombosis with softening
M. . . .	56	Five weeks ago dizziness, headache, paresthesia on left side; recovered in two weeks; later paralyzed on left side; pupils sluggish; aortic disease; speech thick; mental deterioration	4 +	4 +	4 +	240 156	Not done	5544321100	Arteriosclerosis; meningitis; syphilis; softening of left basis pontis and left lobe of cerebellum

F. . . .	58	Ill five months, headaches, dysarthria, girdle sensation, difficulty in walking; right hemiplegia and aphasia	4 +	4 +	4 +	383	Faint trace	5555555432	Multiple areas of thrombotic softening due to meningovascular syphilis
F. . . .	40	Carbuncle followed by erysipelas, then period of excitement and confusion; stupor; neck rigid; no Kernig; reflexes decreased; right pupil fixed; left sluggish	4 +	Neg.	Neg.	0	Neg.	0001100000	Glioma of brain
F. . . .	?	Sick two years; "cold and aches;" past week confused; pupils unequal and fixed; generalized spasticity, catatonic, depressed, hallucinations, disoriented	4 +	Neg.	Neg.	0	Neg.	1223331000	Pellagra
M. . . .	37	Coma, convulsions, paralysis right lower extremity, euphoria, delusions of marital infidelity, auditory hallucinations; alcoholic	4 +	4 +	4 +	30 240	Pos.	1123340000 1123343310	Cerebral syphilis; meningovascular type
M. . . .	56	Epileptic fits for fifteen years; admitted in coma; left pupil rigid; reflexes increased. Bilateral Babinski	Neg.	Neg.	Neg.	0	Neg.	2234322000	Arteriosclerosis of small vessels
M. . . .	60	Numbness in feet, dysarthria, boisterous, profane, threatened to kill wife; spent money foolishly; euphoric, poor memory	Neg.	Neg.	Neg.	8	Trace	0001210000	Arteriosclerosis; multiple areas of softening many small hemorrhages
F. . . .	56	Difficulty in walking; incontinence of urine; stone deaf; pupils small and rigid; no mental symptoms; reflexes increased; bilateral clonus and Babinski	4 +	4 +	4 +	5	Trace	5555555430	Cervical hypertrophic pachymeningitis

TABLE III. GROUP 4.—CASES WITH LABORATORY TESTS SUGGESTING PARESIS BUT NECROPSY FAILING TO VERIFY THAT DIAGNOSIS.

Sex.	Age.	Clinical summary.	Laboratory findings.						Pathologic diagnosis.
			Blood Wassermann.	Spinal Wassermann, cholesterin.	Spinal Wassermann, Neguchi.	Cells per cu. mm.	Globulin.	Colloidal-gold curve.	
F. . . .	60	Pain in stomach for two years; confused, left hemiplegia	Neg.	4+	4+	20	Cloud	2555555544	Syphilitic meningitis
F. . . .	35	Two months prior to death became stuporous, had convulsions of right face	4+	4+	4+	4	Trace	5555554310	Gummatous meningoencephalitis
F. . . .	53	Right hemiplegia one month prior to admission; aphasic, involuntary emotionalism	4+	4+	Not done	8	Trace	5555554310	Cerebral syphilis
M. . . .	48	Stroke at twenty-five, second stroke day of admission; depressed, refused to eat, self-accusatory, incontinent; pupils normal; right hemiplegia	4+	4+	4+	55	Trace	5555543110	Cerebral meningovascular syphilis; aneurysm of basilar artery

F. . . .	33	Ill for one month, drowsy, irritable, depressed; auditory, visual and olfactory hallucinations, violent tremors, pupils unequal, sluggish	4 +	4 +	Not done	95	Not done	5555443100	Softening, left pallidum and right thalamus; meningeo-vascular syphilis
M. . . .	24	Stroke one year prior to admission; second stroke six months later; bedridden, dysarthria, dysphagia, exaggerated deep reflexes	4 +	4 +	4 +	6	Trace	5555554221	Gummatous meningitis and gumma of pons
M. . . .	74	For two months burning in left leg; pupils unequal, irregular, sluggish reaction; gummata of leg; six weeks after admission became stuporous and died	Neg.	Neg.	Neg.	Not done	Not done	5554321000	Left subdural hemorrhage; arteriosclerosis
M. . . .	32	Unconscious with generalized convulsions on admission; fits for eight months previously; pupils irregular and sluggish; left patellar reflex absent	4 +	Neg.	Neg.	20	Cloud	4445443100	Meningovascular syphilis and gumma left parieto-occipital region
M. . . .	42	History and physical signs of tabes, but with bilateral Babinski	Neg.	4 +	Not done	40	Trace	2444432110	Diffuse neurosyphilis
M. . . .	23	Emaciated, prostrated, soon became comatose; cough and expectoration	4 +	Neg.	Neg.	5	Trace	5555542200	Syphilitic endarteritis

While the diagnostician by his too blind adherence to the importance of laboratory examinations may frequently confuse cerebral syphilis with general paresis, it is much more certain that he who diagnoses general paresis without laboratory backing is in greater danger of error. In the cases of Group 3 diagnosed general paresis without strong confirmation by the laboratory, the diagnosis was invariably wrong, although in some of the cases the laboratory in part supported the diagnosis. This is especially so as far as the gold test was concerned. It has frequently been observed that alterations in the colloidal-gold curve are common in many organic affections of the central nervous system. The presence of a paretic or syphilitic curve in the fluid without other evidence of syphilis points rather away than toward the diagnosis of neurosyphilis and particularly paresis.

Another phase of the subject which is of great importance is the correlation of mental symptoms such as depression, irritability, nervousness, excitement, delusions and dementia, with strongly positive evidences of syphilis in the blood and the entire line of syphilitic reactions in the spinal fluid. Some of the cases which we report had positive laboratory tests for syphilis, had definite mental symptoms and yet were not general paresis; but the number of these cases was small. Some of them, however, would defy the most expert clinician in his attempt at differential diagnosis; thus one of our cases in Group 3 had gummas in the left frontal and left parietal regions and softening of the right frontal lobe, paretic findings in the blood and spinal fluid, euphoria, delusions of grandeur, fixed pupils, and hyperreflexia. Who would be so bold as to say that such a case was not general paralysis of the insane? Or consider one of the cases in Group 4: a female, aged 33 years, ill for one month; she was drowsy, irritable, depressed and violent; she had tremors of the face, tongue and hands, the pupils were unequal and sluggish; in addition the patient had auditory, visual and olfactory hallucinations and while there was no history of alcoholism it is not unlikely that she indulged. The laboratory tests pointed strongly to general paresis as the diagnosis. She had softening of the left pallidum and right thalamus and diffuse meningovascular syphilis. Are there many who would have thought that the hallucinations in this case ruled out paresis? We doubt it.

A number of cases with clinical evidence of gross organic disease of the brain or cord and laboratory tests suggestive of paresis proved almost invariably to be cerebral syphilis or other forms of neurosyphilis rather than paresis. While an occasional case showing both mental symptoms and the so-called paretic, laboratory results may be found to be nonparetic; this is certainly not the rule, but it does occur.

Conclusions. Review of the records and the necropsy results in the 67 cases which we report leads us to the following conclusions:

1. An untreated case of general paresis will show blood and spinal fluid evidences of syphilis. These tests will usually be markedly positive, including pleocytosis, an increased amount of globulin and the paretic gold curve.

2. An untreated case diagnosed general paresis without strong confirmatory laboratory backing is practically always something else.

3. A certain limited number of cases showing mental symptoms and evidence in the blood and spinal fluid of a paretic nature may, on microscopic studies of the brains, be proven not to be instances of general paresis.

4. A brain which shows a gross organic condition such as hemorrhage, thrombosis or gumma rarely shows microscopic evidences of general paresis.

5. Strong laboratory evidences of syphilis such as mentioned above without mental symptoms are not enough to allow the diagnosis of incipient general paresis.

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REVIEWS.

CLINICAL APPLICATIONS OF SUNLIGHT AND ARTIFICIAL RADIATION.
By EDGAR MAYER, M.D., of Saranac Lake, N. Y. Pp. 550; 69
illustrations. Baltimore: The Williams & Wilkins Co., 1926.
Price, \$10.00.

THIS book is a most timely one, particularly in view of the efforts being made at this time to standardize this type of work. It contains twenty-six chapters, dealing with the historical, experimental and physiologic action of ultraviolet radiation on animal and plant life. The bibliography is most extensive, representing what one would regard as a lifetime of investigation. The author has presented his research in very good form, and anyone doing this type of work would do well to have the book, which is really an encyclopedia containing all of the experimental work pertaining to this field, with its clinical application in the treatment of disease. The publishers are to be commended upon the paper and print and also the unique way in which they include the various members of their staff, giving credit where credit is due. E. P.

A MANUAL OF PHARMACOLOGY AND ITS APPLICATIONS TO THERAPEUTICS AND TOXICOLOGY. By TORALD SOLLMANN, M.D., Professor of Pharmacology and Materia Medica in the School of Medicine of Western Reserve University, Cleveland. Third edition, entirely reset. Pp. 1184. Philadelphia: W. B. Saunders Company, 1926. Price, \$7.50.

THE rapid advances of pharmacologic investigation are well illustrated in the addition of 120 pages and 1200 bibliographic titles to this edition, in spite of most careful pruning. Numerous new drugs are included, headed by insulin, and various new concepts, together with the tenth edition of the Pharmacopœia, have necessitated rewriting the larger part of the important matter. The book remains of equal value with the previous editions. (See AM. J. MED. SCI., 1923, 165, 285.)

E. K.

PRINCIPLES OF MEDICAL TREATMENT. By GEORGE C. SHATTUCK, M.D., A.M., Assistant Professor of Tropical Medicine, Harvard Medical School. Sixth edition, revised and enlarged. Pp. 256. Cambridge: Harvard University Press, 1926.

THE sixth edition of this work continues its former usefulness. It is a very handy pocket size book and contains a very complete and satisfactory outline of medical treatment. It seems a little overcautious to omit the dose of quinidin sulphate at this late date. Anyone justified in using this book should be trusted properly to employ such a drug.

O. P.

A SOUND ECONOMIC BASIS FOR SCHOOLS OF NURSING AND OTHER ADDRESSES. By MARY A. NUTTING, R.N., M.A., Professor Emeritus, School of Health, Teachers' College, Columbia University. Pp. 372. New York: G. P. Putnam's Sons, 1926.

THE author has been an outstanding leader in nursing education for many years. The present volume puts into permanent form an extreme valuable collection of addresses bearing on the growth and development of schools of nursing. These papers present the findings of the author's own experience in the education of nurses, as superintendent of Johns Hopkins School of Nursing and later as the director of the Department of Nursing and Health at Teachers' College, Columbia University. They are stimulating, outspoken discussions of the dominant problems of nursing education, the root of which is largely found to be economic in nature.

S. G.

PHYSIOLOGY AND BIOCHEMISTRY IN MODERN MEDICINE. By J. J. R. MACLEOD, M.B., LL.D. (ABERD.), D.Sc. (TOR.), F.R.S., Professor of Physiology in the University of Toronto, Can. Fifth edition. Pp. 1054; 291 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, \$11.00.

A NEW edition of the author's textbook—considered by many the best on its subject in English or any other language—is an important event in medical education, and four years is a long time between editions in this rapidly expanding subject. This edition has been made even more valuable to medical students by the addition of a section on the physiology of the special senses by J. M. D. Olmsted and Redfield's section on the neuromuscular system has been expanded to include the extensive field of nerve muscle physiology. One's curiosity is aroused by the position of the neuromuscular system and the special senses between the blood and lymph and the

circulation of the blood. The various additions necessitated the addition of 50 pages and 48 illustrations, without, however, adding appreciably to the unwieldiness of the book. E. K.

PRINCIPLES AND PRACTICE OF CHEMOTHERAPY, WITH SPECIAL REFERENCE TO THE SPECIFIC AND GENERAL TREATMENT OF SYPHILIS. By JOHN A. KOLMER, M.D., DR. PH., D.SC. (HON.), Professor of Pathology and Bacteriology in the Graduate School of Medicine of the University of Pennsylvania and Member of the Research Institute for Cutaneous Medicine. Pp. 1106; 82 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, \$12.00.

In this monograph the author has largely fulfilled his expressed intention of covering the field of modern chemotherapy in all its medical and surgical aspects. The discussion includes sections on general principles, the chemotherapy of bacterial and mycotic diseases, trypanosomal diseases, spirochetal diseases other than syphilis, protozoan and metazoan diseases, and the chemotherapy of anemias, malignant tumors and other conditions of uncertain etiology. Of the 1054 pages, 607 are devoted to the chemotherapy of syphilis, the discussion broadening into the fields of serologic diagnosis, immunologic and pathologic background, technical detail and valuable summaries of the modern refinements of biologic testing and evaluation of antisyphilitic medicaments.

The appraisal of so genuinely monumental a work by a single reviewer must be a matter of great difficulty. One's first impression relates to the author's generally successful effort to illumine an encyclopedic knowledge of laboratory procedure, usually inaccessible or incomprehensible to the clinician, with a by no means narrow clinical experience. That the laboratory furnishes the stronger leg is evident, but the gait and effectiveness of the work for the clinician is not seriously impeded thereby. It is no mean accomplishment to produce a single volume in whose pages can be found a formula for a soothing antiseptic paste for wounds, every known method for the administration of quinin, the germanium therapy of pernicious anemia (even though of doubtful value), a usable technique for getting blood from babies and the malaria inoculation treatment of paresis. As in very work which seeks to harmonize medical knowledge under an artificial or man-made rather than a biologic keynote, one observes occasional strange propinquities.

The author's huge industry, his fairness and completeness of statement, even of opposing views, his excellent critical judgment and scholarly particularity are apparent in every chapter. The

work done in placing the literature of syphilotherapy at the disposal of the clinician would alone justify the book. The development is logical and cohesive, and the discussion of first principles on syphilis forms a particularly sound background for the sadly needed rationalization of modern treatment. If there is any adverse criticism necessary on this point, it is one of insufficient detail on known treatment results in certain phases of the disease.

On many aspects of syphilis the author is qualified to speak *ex cathedra* as an expert of international reputation, and from his comments specialists will glean many points of interest and challenge. His endorsement of arsphenamin (606) as the premier arsenical comes as a breath of relief in a "neo"-saturated world. His evaluation of bismuth, while too brief for enthusiasts, displays a refreshing sanity that the reviewer believes time will fully justify. Mercury is not dead yet! The statements on the clinical relations of the Kolmer Wassermann test will be listened to with respect by every clinician who knows the worth of the author's contributions in this field. The detail of laboratory testing procedure is invaluable, the technical methods in clinical practice adequate and well illustrated, though one cannot but regret the inclusion of the sitting lumbar puncture and the syringe injection of medicaments into the spinal canal.

The book, very properly, is a personal one, but justifiably so, and is kept in excellent balance by the full presentation of the literature. One cannot but wish at times that the bases of the author's own clinical "credos" could have had fuller discussion and a little space for it might have been saved by devices of literary condensation, including a less frequent use of the rhetoric question. The format of the work, perhaps inevitably, because of the volume of material, buries some jewels for the practitioner in the sand of type, and presents at times an unbroken uniformity of face which fatigues the eye. The proofreading is poor, even for so large a book, and will irritate the meticulous.

These detractions are essentially minor. The work will meet the assured and deserved success of a masterly "Arbeit," which accomplishes that only too rare feat in medical literature, of giving rationalizing perspective and usable detail between one pair of boards.

J. S.

ELECTROTHERMIC METHODS IN NEOPLASTIC DISEASES. By J. DOUGLAS MORGAN, B.A., M.D., Instructor in Radiology, University of Pennsylvania Graduate School of Medicine, Philadelphia. Pp. 172; 36 illustrations. Philadelphia: F. A. Davis Company, 1926. Price, \$2.50.

THIS small book is a very timely and concise presentation of the subjects of electrodesiccation and electrocoagulation and satisfies a

need that has long been wished for. It contains nine chapters dealing with the following subjects: Electricity, First Principles and Definitions; Chemical and Physical Effects of Currents; Surgical Diathermy, Its History, Terminology and Uses; Apparatus; Electrodesiccation; Electrocoagulation; General Summary; Tissue Cutting by Means of the High-frequency Current; Practical Exercises in the Use of the Currents. The subjects are well presented and the book is recommended to all who are interested in this particular field.

E. P.

THE PRINCIPLES OF ANATOMIC ILLUSTRATION BEFORE VESALIUS: AN INQUIRY INTO THE RATIONALE OF ARTISTIC ANATOMY. By FIELDING H. GARRISON, M.D. Pp. 58; 26 illustrations. New York City: Paul B. Hoeber, Inc., 1926. Price, \$2.50.

A CHARMING work, full of the author's well-known and unapproachable erudition, in which he shows that the medical man may learn a good deal from the artist. Much physiology, pathology and ethnology, he points out, is exhibited in the paintings and sculptures by paleolithic and neolithic man. The Renaissance artists who made such conscientious dissections seemed, without a direct study of medicine, to understand the physiology of muscular motion and of expression. None was greater in this respect than Leonardo da Vinci.

Both in the entertaining preface and throughout the text the author points out the fact that the true physician must have the artist's vision—the artist's eye to see. The return to the practice of "seeing" and to the independent thinking that goes with it is, in Garrison's opinion, the greatest desideratum of our time. D. R.

BRAINS OF RATS AND MEN: A SURVEY OF THE ORIGIN AND BIOLOGICAL SIGNIFICANCE OF THE CEREBRAL CORTEX. By C. JUDSON HERRICK, Professor of Neurology, the University of Chicago. Pp. 382; 50 illustrations. Chicago: The University of Chicago Press, 1926.

A VERY readable book based on the lectures given in 1924 at the University of California on "Mechanisms of Control of Animal Behavior." It takes up particularly "the two species of mammals whose behavior has been more intensively studied under conditions of laboratory control than any others—rats and men." The evolution of the cerebral cortex from fish to man is considered particularly as regards function. Not only should this book appeal to the Neurologist and Psychiatrist, but to all who are interested in man and his problems.

N. W.

BOOKS RECEIVED.

- Tuberculosis: Bacteriology, Pathology and Laboratory Diagnosis.* By EDWARD R. BALDWIN, M.D., S. A. PETROFF, PH.D., and LEROY U. GARDNER, M.D. Pp. 342; 82 illustrations. Philadelphia: Lea & Febiger, 1927. Price, \$4.50. (To be reviewed later.)
- Nursing Mental and Nervous Diseases.* By ALBERT COULSON BUCKLEY, M.D. Pp. 312; 57 illustrations. Philadelphia: J. B. Lippincott Company, 1927. Price, \$3.00. (To be reviewed later.)
- The Treatment of Chronic Arthritis and Rheumatism.* By H. WARREN CROWE, D.M., B.Ch. (OXON.), M.R.C.S. Pp. 196; 18 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)
- Solubles ou Insolubles.* By HENRI DROUIN. Pp. 96; 10 illustrations. Paris: Paul Martial, 1927.
- Basal Metabolism in Health and Disease.* By EUGENE F. DU BOIS, M.D. Second edition. Pp. 431; 92 illustrations. Philadelphia: Lea & Febiger, 1927. Price, \$5.00. (To be reviewed later.)
- Elementary Bacteriology and Protozoölogy for the Use of Nurses.* By HERBERT FOX, M.D. Fourth edition. Pp. 242; 74 illustrations. Philadelphia: Lea & Febiger, 1927. Price, \$2.50. (To be reviewed later.)
- Outlines of Common Skin Diseases.* By T. CASPAR GILCHRIST, M.D. Pp. 54; 5 illustrations. Baltimore: Williams & Wilkins Company, 1927. Price, \$1.50. (To be reviewed later.)
- The Diseases of Infants and Children.* By J. P. CROZER GRIFFITH, M.D., PH.D., and A. GRAEME MITCHELL, M.D. Two volumes. Second edition. Pp. 1715; 461 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, \$20.00 for two volumes. (To be reviewed later.)
- Clinical Methods.* By ROBERT HUTCHISON, M.D., F.R.C.P., and HARRY RAINY, M.D., F.R.C.P. (EDIN.), F.R.S.E. Pp. 688; 167 illustrations. New York: Paul B. Hoeber, Inc., 1927. Price, \$5.00. (To be reviewed later.)
- A Terminology of Disease.* By ADRIAN V. S. LAMBERT, M.D. Third edition. Pp. 158. New York: Paul B. Hoeber, Inc., 1927. Price, \$2.25. (To be reviewed later.)

- Index and Handbook of X-ray Therapy.* By DR. ROBERT LENK. Translated by T. I. CANDY, M.B., B.Ch. Pp. 121. New York: Oxford University Press, American Branch, 1927. Price, \$2.25. (To be reviewed later.)
- Methods and Problems of Medical Education (Sixth Series).* Pp. 275; illustrated. New York: Division of Medical Education, Rockefeller Foundation, 61 Broadway, New York City, 1927. Continuation of a series useful to medical pedagogues.
- Physicians of the Mayo Clinic and Mayo Foundation.* Pp. 578; 611 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, \$7.00. Contemporary biographies of the Mayo Staff.
- Diseases of the Heart.* By FREDERICK W. PRICE, M.D., F.R.S. (Edin.). Pp. 534; 249 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)
- Heliotherapy.* By A. ROLLIER, M.D. Translated by G. DE SWIETOSCHOWSKI, M.D. Pp. 318; 273 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)
- A Manual of Materia Medica for Medical Students.* By E. QUIN THORNTON, M.D. Second edition. Pp. 384. Philadelphia: Lea & Febiger, 1927. Price, \$4.00. (To be reviewed later.)
- Surgical Applied Anatomy.* By SIR FREDERICK TREVES, BART. Reviews by C. C. CHOYCE, C.M.G., C.B.E., M.D. Eighth edition. Pp. 727; 162 illustrations. Philadelphia: Lea & Febiger, 1927. (To be reviewed later.)
- The Enlarged Prostate.* By KENNETH M. WALKER, M.A., M.B., B.C. Pp. 193; 59 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)
- Symbioticism and the Origin of Species.* By IVAN E. WALLIN, Sc.D. Pp. 171; 2 illustrations. Baltimore: Williams & Wilkins Company, 1927. Price, \$3.00.
- Manual of Operative Surgery.* By SIR HOLBURT J. WARING, M.D., M.B., B.Sc. (Lond.). Sixth edition. Pp. 868; 618 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)
- A Textbook of Clinical Neurology.* By ISRAEL S. WECHSLER, M.D. Pp. 725; 127 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, \$7.00. (To be reviewed later.)
- Manual of Medicine.* By A. S. WOODWARK, C.M.B., C.B.E., M.D., F.R.C.P. Third edition. Pp. 523. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)
- Applied Physiology.* By SAMSON WRIGHT, M.D., M.R.C.P. Pp. 418; 37 illustrations. New York: Oxford University Press, American Branch. (To be reviewed later.)
- Lehrbuch der Geburtshilfe.* By PROF. DR. WILHELM ZANGEMEISTER. Pp. 834; 329 illustrations. Leipzig: S. Hirzel, 1927. (To be reviewed later.)

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

JOHN H. MUSSER, M.D.,

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Diabetes: A Statistical Study of One Thousand Cases.—A statistical study of the patients that have been seen in the last four years by JOHN (*Arch. Int. Med.*, 1927, 39, 67) brings out some interesting data which in part are a confirmation of the statistics obtained by others, but which vary somewhat in some particulars. The statistics include the age and sex, influence of heredity, relation of blood sugar content to glycosuria, the effects of treatment with insulin, the incidence of syphilis in the diabetic, the incidence of operations on diabetic patients and the death rate. Of particular interest are the tables showing the lasting effects of insulin in the treatment of diabetes. It is true that many of these patients have only had insulin for a short time, but it is surprising to find the large number in whom it was possible to discontinue insulin. Another interesting table is the table illustrative of the relation of blood sugar before and at the time of the reaction to insulin. The author shows by his figures that the insulin reaction is not necessarily dependent upon hypoglycemia. In 50 per cent of the cases this was not the cause. In fact, actual hyperglycemia was demonstrated. The author also shows that there is a marked irregularity in the factors that are supposed to play a part in the production of this reaction, as judged by the time relation of the insulin reaction to the dosage of the preparation.

The Mechanism of Pain in Gastric and in Duodenal Ulcer.—The third paper by PALMER (*Arch. Int. Med.*, 1927, 39, 109), in the study of pain in gastric ulcer, deals with the rôle of peristalsis and spasm. It will be recalled that in 1917 Carlson, employing the so-called balloon method showed that intermittent ulcer pain occurred with gastric peristalsis, and he concluded that the pain in this condition was due

to muscle tension. The author investigates Carlson's results and elaborates upon his methods. In addition to the patient swallowing a rubber balloon, he also has him swallow duodenal tubes. Kymographic studies that he has made with this technique are very well done and illustrate very beautifully indeed the reason for his conclusions. He finds that the pain-producing mechanism is intimately associated with ulcer, but it is not dependent upon gastric motility nor upon pylorospasm. At times gastric peristalsis may cause stimulation to the pain-producing mechanism, but probably more important than peristalsis is the direct sensitizing effect of hydrochloric acid, as shown by producing pain when injected into the stomach previously free of gastric contents and when it is withdrawn through the duodenal tube relieving pain.

SURGERY

UNDER THE CHARGE OF

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GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Dislocation of the Semilunar Bone.—McBRIDE (*Arch. Surg.*, 1927, 14, 584) says that reduction of simple dislocation of the semilunar can usually be accomplished by manipulation within the first three or four days and complete return of function can be expected. In cases in which removal of bone is done within two or three weeks, or in which there is mild neurospastic fixation, good function will result, but at least some permanent weakness will remain. Open reduction under the same circumstances promises as good a return of function as removal. There is, however, danger of traumatic arthritis. Untreated patients have from 25 to 75 per cent permanent disability. Open reduction after several weeks or in cases in which neurospastic fixation is severe, should not be attempted, even though in many instances it can be accomplished, for removal is better. Removal in late cases with severe fixation and degenerative changes usually will relieve the pain to a considerable degree, while improvement in function is slight. When fractures of the scaphoid complicate dislocation of the semilunar bone, severe traumatic arthritis is so likely to occur in these cases that closed or open reduction is dangerous. If not accomplished within a few hours after injury, excision is therefore indicated. Removal of the semilunar and whole scaphoid bone seems to give as good results as those secured in cases in which the proximal fragment only is removed and is the method of choice.

Ranula.—FITZWILLIAMS (*Brit. J. Surg.*, 1927, 14, 472) states that ranula is a loose term which has been applied to all cystic swellings of

the floor of the mouth whatever their form or origin. These tumors form first in the mouth and then spread, extend or burrow into other regions. Many are in connection with the submaxillary gland, others are not so obviously in connection with this gland and others again have no connection with it. When traced to the region of the sublingual gland, we have no means of telling whether they are mucous or salivary in origin. It is impossible to test the efficiency of the sublingual ducts. The author has no knowledge of anyone passing bristles into the ducts. Moreover there is no exact knowledge of the number of ducts present in each gland. After full logical deductions the author proves that ranula may arise in the salivary glands, including Blandin's gland, and in the mucous glands and nowhere else. There is nothing to favor the view that Fleischmann's bursa exists and there is nothing to connect a ranula with the supposed survival of a cervical sinus.

Causation of the Increased Intracranial Pressure Associated with Tumors within the Cranium.—STOPFORD (*Brit. Med. J.*, 1926, 2, 1207) says that it is shown that the great vein of Galen is situated in such a position that it may be compressed against the splenium of the corpus callosum indirectly or directly by tumors occupying sites which are known to give rise most constantly to increased intracranial pressure. Such compression is not likely in the case of tumors occupying situations which are known to cause less frequently increased intracranial pressure. Experimental and clinical evidence has been submitted by Dandy and others that occlusion of the great vein of Galen leads to internal hydrocephalus from overproduction of cerebrospinal fluid. It is suggested that moderate compression without complete occlusion of the vein is likely to give rise to increased intracranial pressure, accompanied by slight or negligible dilatation of the ventricles. If the views put forward have been correct the increased pressure caused by intracranial tumors is due to an excessive production of cerebrospinal fluid, the fluid being produced in such quantities that absorption cannot keep pace with production and the intracranial pressure being consequently raised.

Sarcoma of the Bladder.—CECIL (*J. Urol.*, 1926, 16, 490) states that total cystectomy is indicated where the tumor is too large for resection or occupies a position not adaptable to resection. The position of these tumors is most frequently on the base, trigone or vesical orifice, though it is found more frequently on the lateral and anterior walls than epithelial tumors. The gross appearance is not characteristic enough to distinguish it from other tumors. Microscopically the tumors assume all the varieties of sarcoma. They have a great tendency to invade the surrounding structures, and are, moreover, of very rapid growth, not infrequently multiple. They have been found most frequently in the very young or those past middle age, but have been found at all ages. Diagnosis depends entirely upon a microscopic examination of the specimen. Hematuria is not constant and when present is usually a late manifestation. Other symptoms are also late to appear. Radiation has not been tried sufficiently to warrant a conclusion, but will most likely prove inadequate. While resection is the method of choice in early cases, in most cases total cystectomy offers the only chance of cure.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
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Diphtheria Immunization in Providence.—SCAMMAN and POPE (*J. Am. Med. Assn.*, 1927, 88, 563) in three years' experience Schick tested and immunized 15,000 children, and they feel that toxin antitoxin immunization eliminates approximately 90 per cent of the risk of contracting diphtheria in the immunized group. During this time 38 per cent of all the children in the age group five to nine years and 24 per cent of the children in the ten to fourteen years group were immunized. In the group under five years, in which the morbidity and mortality from diphtheria are practically at their height, hardly 4 per cent of the children have been immunized. They feel that to make immunization wholly effective some method must be devised to reach this susceptible group. The health department of the city is sending to the parents of every six months' old child a notice urging immunization by the family doctor or at a clinic. One benefit of diphtheria immunization which cannot be accurately measured is elimination of the spread of the disease by a reduction of the susceptible population. In the spread of a contact disease two factors are essential; cases or carriers of virulent organisms and susceptible contacts. If any increased proportion of the population is already immune, the probability of effective contact between each case of diphtheria and other persons is definitely decreased.

Two Hundred and Forty-three Fetal Autopsies: A Syphilitic Study.—McCORD (*J. Am. Med. Assn.*, 1927, 88, 626) examined 243 infants at autopsy. Only 50 of these had been born alive, 189, or 77 per cent, were born dead and there were 4 abortions about the fourth month. There were 164 premature babies, or 67 per cent. Maceration was present in 45 per cent of the autopsies. Syphilis was positively demonstrated in 45 per cent of the cases; syphilis was probably demonstrated in 20 per cent of the cases. The causes of death in the order of frequency were: Syphilis, 57 per cent; brain hemorrhage and tentorial tears, 13 per cent; prematurity, 11 per cent; toxemia of the mother, 4 per cent. Bone lesion, known as Wenger's disease, seemed to be pathognomonic of fetal syphilis. The lungs, kidneys and liver seemed to be the tissues most frequently involved as evidenced by histologic changes. The spirochetes were found in the tissues in the following order of frequency: Lungs, kidneys and liver. The author feels that negative observations of any kind cannot absolutely exclude syphilis.

The Effect of Irradiated Milk on the Blood.—DAWKINS and PATTERSON (*Lancet*, 1926, ii, 1314) feel that irradiated milk is a greater food value than non-irradiated milk. Their observations were made on five

children who had been in the hospital with active bone tuberculosis for an average period of four months without marked improvement in their general conditions or local lesions. During this period they were given ordinary hospital diet, which included cod liver oil and $1\frac{1}{4}$ pints of milk daily. Later $\frac{1}{2}$ pint of this supply of milk was exposed daily to the rays of a quartz light at a distance of 2 feet for a half hour. The milk was contained in shallow trays and stirred frequently. There was no change in the other diet, but after four weeks the red cells and hemoglobin were found to have increased in four of the cases. The same amount of irradiated milk was continued and at the end of three more weeks the red cells had increased in every case, but the hemoglobin was only slightly changed.

Clinical Manifestations of an Enlarged Thymus.—MORGAN, ROLPH and BROWN (*J. Am. Med. Assn.*, 1927, 88, 703) describe the clinical manifestations in 54 cases which they thought were due to disturbance of the thymic gland. Such symptoms as noisy nasal breathing, hoarse cough, attacks of syncope, restlessness and sleeplessness have not been previously described as being associated with thymic disturbance. The analysis of these symptoms strongly suggests that the cause of their protection is of a mechanical nature, and is most probably due to vagus stimulation. Roentgen ray therapy proved efficacious in relieving the symptoms in 96 per cent of these cases. This form of treatment if not carried to excess is unattended by danger. Recurrence of thymic enlargement or of clinical manifestations was noted in 12, or 22 per cent of the cases. In all these instances further Roentgen ray therapy resulted in complete recovery. Patients showing susceptible symptoms should be given the benefit of Roentgen ray therapy, even in the absence of positive Roentgen ray findings.

Pentosuria.—LEVY and PIERSON (*Am. J. Dis. Child.*, 1927, 33, 212) report a case of pentosuria in a child aged three years. This is the youngest patient on record presenting this type of hereditary anomaly. It would seem that the supposition that the pentosuria was present at birth was accurate. The familial character of the disturbance coincided with other recorded instances. The exact nature of the metabolic disorder is purely speculative. The source of the pentose in this case was not in the diet because, with the exception of the first analysis of the urine, the amount of pentose was extremely constant in spite of dietary variation. Ten specimens examined in a course of about a month contained the following percentage of pentose: 0.24, 0.209, 0.185, 0.209, 0.178, 0.2, 0.209, 0.208, 0.172 and 0.263. The narrow limits in which the output of pentose fluctuated is interesting and there is suggested a comparison with the uniformity of the amount of cystin excreted in cystinuric subjects, which is remarkably constant, varying from 0.3 to 0.5 gm. per twenty-four hours. This is due to the failure of the body to utilize in its usual way some definite part of the protein metabolized. The relationship of pentosuria to diabetes mellitus cannot be dismissed lightly. In this case the pallor and loss of weight following an acute infection might lead one to suspect an existence of a true diabetes, and there was an unusually large output of urine. As a further point in this favor was the fact that the child improved on a diabetic diet together with the administration of insulin.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Syphilitic Paraplegia.—CHUNG (*Arch. Dermat. and Syph.*, 1926, 14, 111) made an extensive clinical study of 34 cases of rapidly developing paraplegia of syphilitic origin, a rather common neurologic symptom complex in China. Two distinct groups are distinguished: (1) An acute type, which develops either overnight or within forty-eight hours, accompanied by a flaccid paralysis with total loss of sensory function below the lesion, with sphincter disturbances and vasomotor changes; (2) a subacute type, which develops more insidiously, associated more often with a spastic paralysis with increased reflexes, more or less disturbances in sensation, sphincter troubles and trophic changes. The pathologic condition underlying these lesions in the acute cases is always thrombosis of one or more important spinal vessels with secondary changes in the cord, and in the subacute cases is also one of thrombosis but with a more widespread meningomyelitis. Recovery is by no means rare. In general, the disease is not rapidly fatal; but the prognosis as to function in protracted cases is grave. Reestablishment of the circulation is largely responsible for the cases of recovery. The use of arsphenamin is necessary to cure the underlying syphilis and to prevent, if possible, further damage to the nervous system.

Vascular Reactions of the Skin to Injury: Some Effects of Freezing of Cooling and of Warming.—In conducting an experimental study of freezing and heating of the skin under controlled conditions, LEWIS and LOVE (*Heart*, 1926, 13, 27) find that the skin begins to freeze when its surface temperature is reduced to a point lying between -2.2° and -25° C. As a result of supercooling the skin may be induced to tolerate a temperature as low as -20.4° C. and a subcutaneous temperature of -9° . Wetting the skin abolishes the supercooling capacity and causes more rapid freezing. Supercooling may occasionally lead to wheal formation, but rarely injures the skin, and skin will show a great increase in capacity for supercooling (that is, tolerance of cold) if it is kept unwashed for some days. (This probably rationalizes from the physiologic standpoint the extraordinary tolerance of certain strata of society for cold.—Rev.) In a further study of livido racemosa and of the response of the cutaneous capillaries to heat, the author (*Heart*, 1926, 13, 153) and his coworkers have advanced the interesting theory that types of telangiectasia in which no histologic abnormality is found are the result of a prolonged or permanent functional vaso-

paresis, such as can be induced by exposure to heat (in the case of livido calorica) rather than to compensatory dilatation of vessels in response to obliteration of others, such as is observed histologically in certain types of telangiectasia.

OBSTETRICS

UNDER THE CHARGE OF

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A Summary of the Midwife Situation in Pennsylvania.—A complete summary of the situation dealing with the midwife problem is given in NOBLE's article (*Atlantic Med. J.*, 1926, 30, 67). The Department of Health undertook the supervision and instruction of these women in eight counties of the State, by permission of the Board of Medical Education and Licensure. The work began in 1922, and was met with difficulties, misunderstanding and resentment; added difficulties were met when the futile Pennsylvania Law, which provides that midwives shall deliver only uncomplicated vertex cases; for any deviation from this rare occurrence the midwife must call a physician. Classes of instruction were given the midwives, consisting of manikin demonstration; there are on record 21,763 deliveries; of these, there were 40 maternal deaths, 611 infant deaths in the first month of life. Most of the work has been done with the foreign population, and the midwives have organized themselves into leagues, fostering pride in their profession. Unless our Immigration Laws change and a large influx of foreigners occurs the midwives will gradually disappear; few new licenses are being granted, and the author states that in all probability the entire group will probably automatically be eliminated in the not too distant future.

Chronic Endocervicitis.—MILLER (*J. Am. Med. Assn.*, 1926, 87, 1695) goes carefully into the embryologic and histologic formation and structures of the cervix, and the function of the cervix is clearly outlined. The importance of endocervicitis and the intrinsic origin along with the multiple clinical findings make this a common gynecologic condition. It must be emphasized that the complicated structure of the cervix, particularly in the light of its frequent exposure to trauma and external infection, make it an ideal location and medium for the growth of bacteria. The etiology is still far from clear. A certain proportion of cases can be attributed to the following: Specific infec-

tion from direct contact, unnoticed childhood infections which have laid dormant for years and to the gonococcus. Much attention has been called to arthritis, nervous and mental diseases and other conditions which have been attributed to the disease of the cervix. Faulty instrumentation, extension of infection upward, following menstruation, chronic constipation, anemia and tuberculosis are among the predisposing factors. Of the infections, all types of bacteria may be identified. Certain types are predominant; of these the gonococcus is most common; streptococcus, the staphylococcus and the colon bacillus are generally agreed to be among the chief bacteria causing the infections. The most constant symptom is leucorrheal discharge. The pathologic picture is for the most part typical. The cervical mucosa appears red, edematous and everted; areas of granular proliferation are adjacent to the external os. The whole is covered with a thick, mucopurulent discharge. Parametritis, posterior cellulitis and sensitive, tender ovaries may be found among a certain percentage of cases. The cervix has been called the tonsil of the pelvis, and much investigation has been undertaken with the idea of identifying it as a systemic focus of infection.

The Clinical Significance of Roentgen Ray Pelvimetry.—THOMS (*Am. J. Obst. and Gynec.*, 1926, 12, 543) points out the principles of the methods used by him and published in 1922, since simplified and improved. The position of the patient and the degree of divergence through which the Roentgen ray passes to the plate is shown. The method is outlined in each step with the patient in the proper position and sketches shown and the Roentgen ray technique is included. This method of Roentgen ray pelvimetry is simple and adds materially to the external diameters and pelvic measurements of the routine pelvimetry in pregnancy, giving us a remarkably accurate measure of the superior strait as well as the other pelvic diameters. The lateral view is of great importance, particularly in deformities of the pelvis. The author so describes the technique that any competent roentgenologist could easily apply it, aiding materially the obstetrician in the diagnosis as well as pelvic measurements.

The Occipitoposterior Position.—A summary of the frequency of this condition and the importance of keeping it before the medical profession until it is better understood is given clearly by BARNES (*Am. J. Obst. and Gynec.*, 1926, 12, 734). As to its frequency as a primary condition there is a wide variance of opinion. The percentages range from 11 to 70 per cent. The problem of the occipitoposterior brings out many methods of delivery and multiple difficulties in handling these cases. The occipitoposterior position is often overlooked, the etiologic factor, the early diagnosis by abdominal palpation and the correct procedure of handling these cases is clearly given to us. The outline of the different methods of treatment and management of these cases is given in detail. Version, rotation, manual and instrumental, Scanzoni method, special instruments are elaborated and the pitfalls and dangers are fully explained.

GYNECOLOGY

UNDER THE CHARGE OF

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Operative Treatment of Cancer of the Cervix.—There are few clinics in this country which have issued reports in recent years on the operative treatment of cancer of the cervix, since radium has largely replaced operation as the therapeutic measure of choice. In Germany, however, there are still a number of surgeons who prefer operation. A report from the clinic of Franz, in Berlin, has been presented by WILLS (*Zentralbl. f. Gynäk.*, 1927, 51, 18), who states that infiltration of one or both parametria is not a contra-indication to operation, provided the bony pelvic wall is not involved, and extension of the cancer to the vaginal walls is not considered a contra-indication. Cancerous invasion of the bladder precludes operation because experience has taught that resection of the involved bladder wall is practically always followed by early recurrence and in many cases by incurable bladder fistulas. There are several constitutional conditions which may contra-indicate operation, such as marked obesity, diabetes, cardiac disease and the age of the patient; in fact, since 1919 no patient over sixty-five years has been operated upon in this clinic. The average age of their patients during the reported five years was forty-four years and one and a half months. During this period Wertheim operations were performed upon 296 women, of whom 12 were sixty years or older. Of these 12 there was a 50 per cent mortality and only 1 of the patients lived four years after the operation. Of the entire series the carcinoma was confined to the cervix in only 15.5 per cent. The primary mortality averaged a trifle over 14 per cent and 133 of the patients (44.93 per cent) were alive after five years. If only the early cases are considered the primary mortality was 6.5 per cent and 76 per cent of the patients survived five years, while the mortality of the borderline group was 29 per cent. There were 4 patients in the series who were pregnant in addition to having carcinoma, and it is their belief that the carcinoma should be operated upon as soon as possible without regard for the pregnancy unless the carcinoma is inoperable and the pregnancy is older than thirty-five weeks, in which event the end of gestation should be awaited. In the 4 cases in this series (pregnancy at two, three, five and eight months) the radical Wertheim operation was undertaken in all; in the last case, after the child was delivered by Cesarean section, the mother dying of peritonitis. Two of the other patients died of recurrences, while the fourth patient is free from recurrence after seven years. The vaginal operation of Schauta has been performed only twelve times during the period reported. They

feel that it has a very limited place in the treatment of cervical cancer, and should be reserved for the obese and aged patients. The following table which briefly shows the results obtained in this clinic by means of the Wertheim operation will be of interest:

Year.	No. of operations.	Primary mortality.	Alive after five years.
1916	45	5 (11 per cent)	17 (38 per cent)
1917	38	3 (8 per cent)	18 (47 per cent)
1918	84	15 (18 per cent)	31 (37 per cent)
1919	63	9 (14 per cent)	30 (48 per cent)
1920	66	10 (15 per cent)	37 (56 per cent)

Bilateral Pyelograms.—Most gynecologic urologists have been hesitant about making pyelograms of both kidneys at the same time because of a fear of possible serious renal impairment. This fear is not justified according to MATTES (*J. Am. Med. Assn.*, 1927, 88, 17), who describes his results with the use of 40 per cent sodium iodide solution by what he terms the "flat sac method." According to his technique no purgatives or enemas are ordered so as to avoid any tendency to reflex irritative phenomena. The use of small catheters permits of lateral drainage, does not block the ureter and does not disturb the waves of contraction, particularly in cases of ureteral strictures and ptosed kidneys. The high concentration of the solution permits dilution by the urine, without affecting its ability to cast a shadow. The catheters are passed to the pelves, or as far as they will go. Each side is aspirated and the amount of fluid withdrawn noted. A plain picture is first made showing the course and relations of the catheters. The second roentgenogram follows the injection of each pelvis with from 3 to 4 cc. of fluid. If any pain is elicited or any symptom noted the injection is discontinued on that side and an approximate amount instilled on the opposite side. The catheters are plugged during the taking of the pyelogram. The cause of any reaction may be due to the catheter end being in the calix, to the unusual smallness of the pelvis, to some pathologic condition or to a contraction of the pelvis during the moment of the injection. The instillations are made fairly rapidly, within from four to eight seconds. The points that he emphasizes are that the capacity of the renal pelvis is small and that if small catheters are used and the injections quickly made, using a high concentration solution, there is very little danger in making simultaneous bilateral pyelograms.

Relation of Nerve Supply to Ovarian Function.—In his endeavors to determine the relationship, if any, between the nerve supply and the function of the ovary MACOMBER (*Boston Med. and Surg. J.*, 1927, 196, 21) performed two sets of experiments upon rats. In the first experimental study the nerve to one ovary was divided and a section of the nerve removed, while in the second set of experiments sections of the nerves to both ovaries were removed. These animals were then bred and the effects upon fertility were noted. The results proved conclusively that the nerve supply to the ovary is not necessary to the function of normal reproduction. They also show that the sterility produced by dividing the ovarian artery, veins and nerves in a previous set of experiments was not due to any interference with the nerve

supply. Previous experiments in which the ovarian artery alone was divided without producing any notable amount of sterility had shown that the interference with the arterial circulation alone could not be considered responsible. By exclusion, therefore, this experimental sterility would seem to be due to some interference with the venous return from the ovary. Such a supposition is the more reasonable to the author, as it is well known in human surgery that interference with the venous circulation will often lead to the development of a cystic condition in the ovary.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Interstitial Keratitis of Dental Infection Origin, with the Report of an Interesting Case.—MACKENZIE (*Med. J. and Record*, 1927, 125, 85) reports the case of a man, aged sixty-four years, who had a severe and painful, nonsuppurative keratitis and iritis of the right eye, which had been diagnosed as interstitial keratitis and treated as such by antiluetic remedies for five weeks by an ophthalmologist, with no results. There was a loss of the normal transparency of the cornea due to the presence of a grayish infiltration in the corneal stroma covering approximately half of the cornea. The deepest infiltration was in the center of the cornea, leaving the periphery fairly clear. The left eye was not affected nor were there any stigmata of hereditary lues. Several alveolar abscesses were found by Roentgen ray in edentulous areas. After surgical treatment had successfully cleared these areas of infection the ocular inflammation subsided and the cornea gradually became clearer, with vision equal to 6/10. The author states that "interstitial keratitis, which is generally assumed to be of syphilitic origin, can be due in rare cases to a focal infection." Interstitial keratitis of syphilitic origin is practically always bilateral, whereas when due to focal infection it is generally unilateral.

Keratitis as a Complication of Dengue Fever.—RICHARDSON (*South Med. J.*, 1927, 20, 32) observed three cases of keratitis, a rare complication of dengue fever, the first symptom of ocular complication of hyperesthesia of the cornea. After the first few hours of hyperesthesia the affected area of the cornea becomes anesthetic, and this anesthesia persists for some time, in one case more than two months. In the cases in which the keratitis developed during the attack of fever, the superficial ulceration was more extensive and the iris very irritable, requiring the continued use of a mydriatic. Postdengue keratitis is evidently due to peripheral neuritis of the portion of the corneal nerve plexus corresponding to the affected area, with resulting keratitis neuropara-

lytica. Ocular symptoms prominent in the active stage are intense aching of the eyeballs, supraorbital neuralgia, sensation of tension within the globe, pain with ocular movement, lacrymation, photophobia and burning sensation of the conjunctiva. Blepharospasm is associated with mild or severe injection of the conjunctiva. Bacteriologic examination of the secretions of the conjunctiva are negative. Intraocular tension is normal. Pupils and pupillary reflexes are normal. Three cases of unilateral herpes of the eyelids were seen in the same group of dengue fever cases. In addition, two of these showed herpes of the lips and one of the alæ of the nose. In a discussion of this paper, Gill stated that ocular complications of dengue fever are as follows: (1) Retrobulbar pain considered due to myositis of the extraocular muscles, present in every case; (2) conjunctival congestion or suffusion of varying degree, always present; (3) congestion of retinal veins thought to be due to cerebral congestion; (4) weakness of accommodation resembling that after diphtheria, but of shorter duration. No extraocular paralyses were found in 1241 cases, nor was there a case of keratitis in the group.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Radium in Polypoid Ethmoiditis.—Among the diseases encountered by the rhinologist, one of the least amenable to treatment is hyperplastic ethmoiditis with polypoid change. While the etiology of this condition is still in question it is generally conceded that irritation plays an important rôle, but it has not been determined that it is the predominant one. McCULLAGH and ROBINSON (*Arch. Otolaryngol.*, 1926, 4, 215) believe that ethmoidal polypi seldom develop in cases that are frankly purulent from the start; they call attention to the frequent association of asthma with ethmoid disease as an added factor which should be a further incentive to stimulate search for a truly causative agent. Formerly the sole method of attack has been surgical, the results having been gratifying neither to the patient nor to the surgeon. The authors have supplemented the surgical procedure—performed as completely as possible—with the introduction of radium. The radium is inserted into the ethmoidal area in a tube (50 mg. for two hours or 100 mg. for one hour) and repeated within ten days or two weeks. The dosage varies in the individual case, the average condition receiving four applications, or approximately 400 mg. hours. The gamma rays are used, the beta rays being screened off by 0.2 mm. platinum and 1 mm. brass. Sixteen cases were so treated, 12 of which had a preliminary complete ethmoidectomy. All patients were markedly benefited subjectively, although the authors do not claim a definitive cure

in any. They believe their experiences with this method corroborate the conclusions of the reports of Sluder, and of Lyons, both pioneers in this field.

Nonendoscopic Cases of Foreign Bodies in the Tonsil.—"Among the many foreign bodies found in the faucial and lingual tonsils and in the lymphoid tissues of the pharynx, fish bones are more common than all the other forms combined. Other substances, such as toothbrush bristles, toothpicks or slivers of wood, spicules of some of the long bones, plant stems and occasionally some form of metallic foreign bodies, are found." In his dissertation upon this subject, CLERF (*Arch. Otolaryngol.*, 1926, 4, 489) states that it is safe to assume that carelessness in the preparation and in the eating of food is the most important factor in their occurrence. According to Jackson, carelessness is responsible for the presence of foreign bodies in the air and food passages in 87.2 per cent of cases. Individuals wearing complete dentures, which deprive them of the protective sensations of the parts they cover, frequently are afflicted with foreign bodies. Rapid eating, with bolting of food, and hypertrophic and protruding tonsils predispose to foreign body lodgment. Sharp, sticking pain, intensified by swallowing, is a prominent symptom. Although the power of localization about the tonsil region is poor, it is useful in determining the side affected. Diagnosis depends on the history and a thorough, systematic search, using an angular pillar retractor. If inspection fails, palpation is a valuable adjunct. Roentgenology is invaluable if the foreign body is in the esophagus or the hypopharynx. Removal by forceps, followed by colloidal or inorganic silver applications, constitute the treatment. In cases where the foreign body has been proved to be buried in the tonsil, tonsillectomy should be done.

The Alkaloids of *Ceanothus Americanus* and their use in the Control of Hemorrhage in Laryngology.—Although reference to the use of *Ceanothus americanus* as a "styptic for restraining hemorrhage from wounds" has been found as far back as 1836, and the work of CLARK (*Am. J. Pharm.*, 1926, 98, 147) indicated several distinct advantages of this drug over others now in general use as hemostatics, PAYNE (*Ann. Otol., Rhinol., and Laryngol.*, 1926, 35, 769) was unable to find "any work in the literature covering the clinical observation of this drug as a coagulant." Accordingly, he reports his observations of a standardized solution containing 1 mg. of the mixed alkaloids of *Ceanothus americanus* per cubic centimeter on the coagulation time of 234 cases, most of whom received a dose of 15 cc. by mouth. The coagulation time of the blood was determined by the capillary-tube method. Following the oral administration of the solution there was a consistent depression in coagulation time, amounting to an average of 21.9 per cent in 225 cases in which the clotting time was normal or low. The shortening of the coagulation time began within fifteen minutes after the administration of the solution and reached its maximum in about forty-five minutes. Age or sex of the patient did not influence the coagulant action of the drug. In 8 instances whose average coagulation time was 9.68 minutes the average reduction in clotting time was 50.6 per cent within an hour after the drug had been given. There was practically no postoperative bleeding in these cases.

RADIOLOGY

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Roentgenologic Diagnosis of Disease of the Uterus and Adnexa.—NAHMMACHER (*Fortschr. Roentgenol.*, 1926, 35, 579) has employed uterosalpingography with iodopin in fifty cases, and writes with enthusiasm of its value, not only in the diagnosis of sterility but of many other conditions. His illustrations are numerous and striking. In metritis the uterine cavity is greatly enlarged with smooth contours, and the cervical canal is broadened. Polyps and submucous myomas produce characteristic filling defects in the iodopin shadow. In ovarian tumor the mass is surrounded or partly surrounded by the tube and the uterus is displaced. The picture of uterus bicornis is characteristic. Employment of the method is contraindicated by acute inflammations, fever, pregnancy and gonorrhea, but not by hemorrhage.

Family Diverticulosis of the Colon.—MACKOY (*Radiology*, 1926, 7, 408) reports 8 members of a family, in three generations, who suffered from a chronic intestinal trouble which presented similar clinical pictures in all cases. By Roentgen ray examination the diagnosis of diverticulitis of the colon was established in 2 of the cases (sisters) and a symptomless diverticulosis was demonstrated in a third sister. In 1 of the 3 patients more than 100 diverticula of various shapes and sizes were revealed.

Diagnostic Inflation of the Knee Joint.—BERNSTEIN and ARENS (*Radiology*, 1926, 7, 500) describe a method of inflating the cavity of the knee joint with carbon dioxid for roentgenography. They feel that the method is of substantial aid in the diagnosis of tears of the ligaments, displacements and tears of the cartilages and chronic synovitis. They have employed it in about fifty cases without untoward results.

Roentgenologic Diagnosis of Congenital Disease of the Heart.—ARKUSSKI (*Fortschr. Roentgenol.*, 1926, 35, 455) believes that every congenital cardiac lesion has a certain corresponding Roentgen picture. In a case of open ductus Botalli the roentgenogram revealed a characteristic hypertrophy of the left ventricle with protrusion of the arch of the pulmonary artery. In a case of stenosis of the pulmonary artery the right ventricle was enlarged and the arch of the artery was flattened. The clinical diagnosis of patent ductus Botalli was shown to be erroneous in one case, the actual lesion being pulmonary tuberculosis, and in another patient the diagnosis of defect in the ventricular septum was disproved, luetic mesaortitis being found.

Roentgen Therapy of Syringomyelia.—STORMER and BREMER (*Fortschr. Roentgenol.*, 1926, 35, 547) report the results of Roentgen therapy in 9 cases of syringomyelia. Improvement was marked in 3 patients, 3 were slightly improved and 3 remained unchanged. Thirty per cent of the erythema dose was given, and repeated twice at intervals of two or three days, followed by another series after five weeks.

Resolution in Pneumonic Consolidation.—ALLISON (*Am. J. Roentgenol. and Rad. Therap.*, 1926, 16, 549) quotes with approval Giffin's opinion expressed twelve years ago as to the great accuracy of the Roentgen ray in excluding pulmonary tuberculosis. The author feels also that with the Roentgen ray more early tuberculosis is recognized now than ever before, but he believes, nevertheless, that the percentage of nontuberculous lesions diagnosed with the Roentgen ray as tuberculous is higher than it was ten years ago. The earliest Roentgen sign diagnosis of tuberculosis is the typical mottling first described by Cole. Signs are present at an earlier stage than this but they are not pathognomonic. Remarkable resolution, even to complete disappearance of a tuberculous lesion, can take place in a very few months.

Diseases of the Chest Demonstrated by Lipiodol.—PIRIE (*Am. J. Roentgenol. and Rad. Therap.*, 1926, 16, 553) has had experience with seventy-seven injections of lipiodol into the lungs for roentgenologic examination. No ill effects followed save in one instance, a patient who had advanced bilateral tuberculosis with pneumonia, and who died of acute cardiac dilatation during injection. Lipiodol produces a pathognomonic Roentgen picture in bronchiectasis. Among other conditions in which its employment is indicated are: Suspected tuberculosis when bacilli cannot be found, after thoracoplasty, for demarcation of the diaphragm in suspected subdiaphragmatic abscess, for localization of a known pulmonary abscess, for stenosis, for bronchopleural fistula and for foreign bodies. In skilled hands bronchoscopic injection of lipiodol is the best method.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Idiopathic Narcolepsy.—ADIE (*Brain*, 1926, 49, 3), writing on this interesting subject, begins his article with the definition, "a disease characterized by the occurrence of attacks of irresistible sleep without apparent cause, and curious attacks on emotion in which the muscles relax suddenly, so that the victim sinks to the ground fully conscious

but unable to move." The author bases his description of this disease upon an analysis of 6 of his own cases as well as upon 15 cases previously reported. He feels that true narcolepsy is a distinct disease and objects to considering this disease as an epileptic or as a functional condition. He gives excellent case histories that bring out the following facts regarding this disease: (1) Sex, duration and treatment; narcolepsy is especially confined to the male sex—17 cases occurred in this sex to 3 in female sex. (2) Age at onset varied from thirteen and a half to thirty-nine years. The usual statement that this disease always begins at puberty is incorrect, according to the author. The duration of the disease varies from six months to twenty-one years. All forms of treatment have been tried without success, including the use of the bromids, thyroid extract, caffein and other drugs to prevent sleep. Hospitalization made the attacks less frequent, although they recurred with original frequency after discharge. In regard to the family history, there is no evidence that heredity plays an important factor. In general, the patient's mental conditions were normal. The laboratory examinations, including spinal fluid examinations, were normal. Two kinds of attacks occur, the sleep attack and cataplexy. The sleep attacks varied in duration from a few seconds to forty minutes. The patients passed into a condition resembling normal sleep and were usually easily awakened. Attacks occurred while the patient was walking, riding or cycling, on the march, during bombardments. One patient fell asleep driving his car. Another patient fell asleep while dancing. Auræ often occurred, consisting of fatigue and discomfort in frontal region. Some patients can resist the inclination to sleep. Attacks vary in frequency from two to three per day. The cataplectic attack may be brought about by any emotion, especially by hearty laughter and anger. Attacks occurred in the anticipation of enjoyment, especially in the theater. The patient's limbs become flaccid and he falls, unable to talk, without losing consciousness. Cataplectic attacks can be avoided by refusal to laugh. Cataplexy in narcolepsy is as characteristic of the disease as the sleep attacks. The author differentiates this disease from epilepsy, pyknolespy, hysteria and all other diseases in which excessive sleep occurs. Narcolepsy should never be used as a symptom of many dissimilar conditions. True narcolepsy may follow an attack of encephalitis lethargica. The combination of sleep attacks and cataplexy, with the above exception, does not occur in any other condition. Narcolepsy is considered by the author to be a disease of the pituitary and adjacent vegetative centers in the floor of the 'tween-brain which form an endocrine nervous system. He discusses Pavlov's conception of normal sleep and produces evidence to support the above localization.

The Constancy of the Intelligence Quotient of Mental Defectives.— A study and reëxamination of 441 feeble-minded persons who had been inmates of an institution for periods varying from two to ten years made by MUROGNE (*Ment. Hyg.*, 1926, 10, 751) showed a marked constancy in their intelligence quotient. In 72 per cent of the cases no change was noted. In 24 per cent there was a loss and in 5 per cent a gain. Ninety-one per cent showed a variation of no more than 10 points. The greatest frequency of variation was in children under

twelve years of age. Males show more variation than females and their change tended to be a loss. No explanation of the variations appeared in these studies.

A Note on Type of Onset in Relation to Clinical Type in General Paresis.—BUNKER (*Am. J. Psychiat.*, 1926, 6, 119) states that very little correlation exists between the type of onset and the clinical type of general paresis which develops with the exception of the "manic" cases. In a study of 74 cases of general paralysis, 57 first showed abnormalities in the emotional sphere in one of two forms—either as irritability or a seclusive apathetic reaction. All of the "manic" cases developed from those individuals having an "irritable" type of onset. Early loss of weight, increased tendency to sleep and in some cases forgetfulness were without significance as to the subsequent clinical type (dementing simple or "manic"). Of 11 patients with early speech defects, all but 1 fell in the category of simple dementing cases.

PATHOLOGY AND BACTERIOLOGY

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The Basic Concepts of Immunity.—The Ehrlich theory as to the origin and nature of antibodies has had wide acceptance and, although frequently attacked as fantastic, the terminology of immunologists would indicate that this hypothesis is still largely held. MANWARING (*J. Immunol.*, 1926, 12, 177) believes it would be wise if we would quietly lay aside for future reference the entire scheme of immunology based upon the specific receptor hypothesis, and considers it probable that the prominence given to this theory constitutes today our most serious handicap to immunologic progress. The mystery of the origin and nature of antibodies may be unraveled by directing attention to the normal and pathologic permeability of fixed tissues and wandering cells for immunologic antigens and to the interplay of antigens with extracellular and intercellular, hydrolyzing and synthesizing enzymes. Physiologic facts developed in his laboratory suggest that the fundamental Ehrlich concepts are at least problematic. There is no direct experimental evidence either for or against the three major hypotheses of the Ehrlich theory, but the indirect experimental evidence is contrary to certain deductions logically drawn from the theory. The fixed tissues of an immune animal, freed from circulating antibodies, should

necessarily be hypersensitive, due to an increased number of sessile receptors. This was not found to be true by experimental test and similarly with a number of other deductions. The author thinks that a consistent theory of immunity may be based on the assumption that antibodies are slowly synthesized in the body by the action of synthesizing enzymes, and by them specifically adapted to injected antigens or to products of antigen hydrolysis. Such an assumption is more nearly in accord with the known facts of cellular biology, and it would, also stimulate the hope that in time therapeutic antibodies may be successfully synthesized in the chemical laboratory.

Pulmonary Neoplasms.—ATKINSON (*Am. Rev. Tuberc.*, 1926, 14, 556) concludes that primary malignant tumor of the lung has increased decidedly in recent years, and this increase is out of all proportion to the general increase in cancer incidence. Heretofore, lung neoplasms have not offered a fertile field for treatment because only secondary tumor deposits have ordinarily been recognized, and when primary neoplasm has been diagnosed the growth has usually been so far advanced as to offer little chance for successful attack. Lung tumors are most frequently diagnosed as tuberculosis. Since pulmonary malignant tumor is now known to be definitely on the increase, special efforts should be put forth to detect the condition at an early stage.

Information on Streptococci.—Recognizing that there are many divergent views on the differentiation, transmutation and virulence alteration of streptococci, WIRTH (*Centralbl. f. Bakteriol.*, 1926, 99, 266) undertook a careful study of some twenty tests on 171 strains of streptococci, including pneumococci. By these tests he divided his cultures into eight different types, and with the characters thus determined he studied the hemolysis on blood agar and the mouse virulence, both of which were found to be capable of alteration. He does not consider that there has been reported up to date a single example of unequivocal transmutation of one type of streptococcus into another type. The bactericidal test, using blood of healthy humans, was found to indicate the relative virulence of his strains for mice. He could not, however, confirm the work of Ruge, Philipp and others, who claimed that the multiplication of a strain of streptococcus in the blood from a patient indicated an unfavorable prognosis. His work dealt with infections of the throat and ear, while the others had to do particularly with the genital tract. On the other hand, the local injury of tissue he believes to be the determining factor in the prognosis, since damaged tissue was found experimentally to increase the virulence of injected hemolytic streptococci, and the mere presence in an infected site of streptococci, capable of growing in the blood of a healthy or diseased person, does not in itself indicate what the outcome may be. This is a valuable contribution to the study of streptococci.

Experimental Production of General Peritonitis.—STEINBERG (*Am. J. Path.*, 1926, 2, 415) states that there are three general methods employed to produce experimental peritonitis: (1) Intraperitoneal injection of microorganisms; (2) perforation of bowel; (3) ligation of appendix. White rats, guinea pigs and rabbits succumb rapidly to

intraperitoneal injection of fairly virulent bacteria, while cats and dogs do not. But when gum tragacanth is added to a culture of *Bacillus coli* and injected intraperitoneally into dogs, they succumb. Ligation of the appendix produces death in forty-eight hours in the majority of animals. The author and Ecker seldom found any pathologic changes in the peritoneum of rabbits receiving *Bacillus coli* antiserum intravenously and then given *Bacillus coli* intraperitoneally. But *Bacillus coli* antiserum and an equal amount of twenty-four-hour *Bacillus coli* broth culture mixed, and injected intraperitoneally into rabbits, produced acute and healing peritonitis. The free peritoneal exudate contained fibrin and a great many polymorphonuclear leukocytes, but the fixed tissue reaction was predominantly mononuclear in type. Benians injected rabbits intravenously with small numbers of *Bacillus coli* to produce active immunization, and found that subsequent intrapleural injection of a lethal dose of *Bacillus coli* produced no ill effects.

HYGIENE AND PUBLIC HEALTH

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Measles Prophylaxis.—TOWNSEND (*Boston Med. and Surg. J.*, 1926, 194, 869) used prophylactic measures in an epidemic of 63 cases of measles in a boarding school of 400 boys. A dosage of blood from an adult who had had measles twenty years previously appeared to have no effect in preventing or modifying the disease. Blood from convalescents had little or no effect in preventing infections, but markedly influenced the course of the disease when given before the end of the first week of the incubation period. Thirty-two cases inoculated with convalescent blood at least eight days before development of the rash showed an average duration of the febrile period of 3.66 days, with a maximum temperature of 102.5°, whereas 21 boys who received no inoculation showed an average duration of the febrile period of 6.45 days and a maximum temperature of 103.5°. The average stay in the infirmary of the 32 inoculated boys was 9.7 days, whereas the average stay of the control group was 13.6 days. The mild character of the disease in many of the boys who were inoculated was very evident and among them absolutely no complications occurred, while in the control group of 21 there was 1 case of bronchopneumonia, 1 of otitis media, 1 of frontal sinusitis and 1 of external otitis. The inoculations had no ill

effects whatever. Beneficial effects were obtained whether the blood was administered as late as six days after exposure or as early as twelve days before the probable date of infection.

The Relation of Endemic Goiter to Certain Potential Foci of Infection.—OLESON and TAYLOR (*Pub. Health Repts.*, 1926, 41, 557) give the following summary and comments: (1) Examinations were made of the teeth and tonsils of 1341 white boys and 1576 white girls in eight schools in Cincinnati for the purpose of determining whether there was a relationship between potential foci of infection and thyroid enlargement. (2) Records were kept of slight and marked thyroid enlargements as well as of slight and marked decay of teeth; in addition, there were recorded the number of apparently normal tonsils, the absence of tonsil through operation, hypertrophy and cryptic degeneration. (3) Slight thyroid enlargements prevailed to the extent of 37.2 per cent among the boys and 50.4 per cent among the girls; both moderate and marked enlargements were approximately seven times more prevalent among the girls than among the boys. (4) In the group studied slight and marked dental decay is no more characteristically associated with thyroid enlargement than with normal thyroid status; furthermore, the degree of thyroid enlargement appears not to be dependent upon the amount of dental decay. (5) Normal tonsils were found more frequently among both boys and girls with thyroid enlargement than among those with normal thyroids. (6) Approximately one-third of the children examined had had their tonsils removed by operation; a slightly greater percentage of thyroid-normal children had had their tonsils removed than those in whom the thyroid was enlarged at the time of the examination; while differences may be noted in the several age groups as regards absence of tonsils, removal often being associated with a higher percentage of thyroid-normal individuals, the evidence is suggestive rather than striking. (7) Enlargement of the tonsils was found more frequently among boys and girls without thyroid enlargement; while some of the evidence concerning hypertrophy of the tonsils in the several age groups is suggestive, the data are too uneven in trend to be convincing. (8) There was no consistent evidence of correlation between cryptic tonsils and thyroid status. (9) Marked thyroid enlargements among the girls are not associated with enlarged or cryptic tonsils as often as are slight thyroid enlargement. The size of the thyroid enlargement is probably independent of tonsillar or dental conditions. (10) Based upon the material gathered during the present investigation, it is believed that there is no definite relations between thyroid status and potential foci of infection presumably located in decayed teeth and enlarged or cryptic tonsils. Comment: The number of children included in the present survey was small and the observations were subject to manifest limitations. Before the relationship between thyroid enlargement and potential foci of infection in the teeth and tonsils can be regarded as definitely determined it is desirable that additional studies be made in other sections of the country on a more comprehensive scale and possibly with different methods. Nevertheless it is felt that in so far as the present study is concerned, such a relationship is nonexistent. Despite these negative findings, neglect of oral hygiene is not advocated. On the con-

trary, renewed efforts to insure as nearly perfect denture as possible, through appropriate nutritional guides and practice, as well as competent dental prophylaxis and treatment, are recommended and urged. Moreover, appropriate treatment for enlarged and diseased tonsils is likewise advised.

PHYSIOLOGY

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SESSION OF MARCH 21, 1927

The Production of Heterophile Antibody by Acid-fast Bacteria.—J. D. ARONSON and C. F. ARONSON (from the Henry Phipps Institute, University of Pennsylvania). The serum of rabbits injected with suspensions of the organs of guinea pig, horse, dog, cat, mouse or turtle will hemolyse sheep cells. On the other hand the serum of rabbits injected with the suspension of the organs of rabbit, sheep, goat, man, ox or rat lack this property.

The antibody produced by the injection of the organs of the first group of animals has been termed heterophile antibody while the antigen has been termed heterophile antigen.

The heterophile antigen is soluble in alcohol and is not affected by prolonged boiling. It gives a positive complement reaction with heterophile serum and produces a precipitate with the serum. The alcohol soluble fraction is the specific fraction of the antigen but when injected into animals does not produce heterophile antibody. The addition of protein to this fraction is essential for the production of heterophile antibody.

Heterophile antigen has been found in *B. dysenteriae* (Shiga), and in one of twelve strains of *B. leptosepticum*.

In this study the occurrence of heterophile antigen in the various acid-fast bacilli was determined. Immune sera were prepared by repeatedly injecting rabbits, intravenously, with suspensions of the various acid-fast bacilli. The animals were bled to death ten days after the last injection and the sera collected and heated at 56° C. during thirty minutes. The amount of heterophile antibody present in the various sera was determined by adding to various amounts of the different sera two units of fresh guinea pig complement and 0.1 cc. of a 5 per cent suspension of sheep cells. Readings were taken after thirty minutes incubation and again after standing overnight in the ice box.

No heterophile antibody was present in the serum of the rabbits which had been injected with the human, bovine or avian type of *M. tuberculosis* or with the following acid-fast mycobacteria: *M. leprae* (Clegg), *M. leprae* (Duval), *M. leprae* (Kedrowski), *M. butyricum*,

M. "milk," M. butter (Korn), *M. butter Rabinowitch*, *M. Rabinowitch*, *M. smegmatis*, *M. mist*, *M. paratuberculosis*, *M. pseudoperlsucht*, *M. marinum*, *M. chelonci*, *M. marpmann*. On the other hand the serum of the rabbit immunized with a culture of *M. phlei* was found to hemolyze sheep cells in a dilution of 0.001 cc. to 0.0005 cc. The heterophile nature of this antibody was further studied by means of the complement-fixation reaction and by absorption experiments. It was found that the serum gave a positive complement-fixation reaction with an alcoholic extract of guinea pig kidney but the reaction was negative when alcoholic extract of beef heart was used. The heterophile antibody present in the immune serum of *M. phlei* was absorbed by unheated and heated sheep cells but not by unheated or heated human cells.

An experiment was carried out to determine whether heterophile antigen is produced by acid-fast bacilli when grown on Long's synthetic medium. Cultures of *M. phlei*, *M. lepræ* (Clegg), *M. milk* and *M. paratuberculosis* inoculated on this medium and incubated during two weeks were filtered through filter paper and the filtrate treated according to the method of Hopkins and Pincus for crystallizing egg albumin. The resulting precipitate was dialyzed and rabbits were injected repeatedly with the nondialyzable residue. In the serum of the rabbits injected with the nondialyzable residue of *M. phlei*, *M. milk* and *M. lepræ* (Clegg) no heterophile antibody was found while the serum of the rabbit injected with the nondialyzable residue of *M. paratuberculosis* in a dilution of 0.001 cc. to 0.0005 cc. hemolyzed sheep cells. This serum gave a positive complement-fixation reaction with an alcoholic extract of guinea pig kidney but the reaction was negative when an alcoholic extract of beef heart was used as the antigen. The heterophile antibody present in this serum was absorbed by unheated and by heated sheep cells but not by human cells.

Lactic Acid in the Blood after Experimental Hemorrhage, and after Injection of Sodium Lactate in Dogs.—CECILIA RIEGEL (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania). After severe hemorrhage there is a decrease in pH and in the alkaline reserve of the blood. These changes have been attributed by some to an increased production of lactic acid by the body, and by others to diffusion of alkali from blood to tissues. The experiments here reported support the first possibility.

Increased formation of lactic acid may occur when the oxygen supply to the tissues is inadequate. The transport of oxygen may be diminished after hemorrhage on account of constriction of peripheral blood-vessels, and the decrease in hemoglobin due to removal of a portion of the blood. We might expect, therefore, an increase in production of lactic acid after hemorrhage, resulting in an increased concentration of lactic acid in the blood. In order to study this possibility experiments were made in which normal dogs were bled 30 to 40 per cent of the blood volume. After hemorrhage samples of blood for analysis were taken at various intervals. In every case there was an increase in the concentration of lactic acid in the blood, the amount depending upon the extent of hemorrhage. When the hemorrhage was not extreme the highest lactic acid concentration was found at the end of the bleeding, followed by a gradual return to normal. When the hemor-

rhage was severe the lactic acid continued to increase for one to one and a half hours, and then began to return to normal. The decrease was always gradual. It depends upon restoration of an adequate oxygen supply, which prevents further formation of lactic acid, and upon the rate at which the chemical reactions involved in the removal of lactic acid proceed.

The disappearance of lactic acid from the blood after hemorrhage and after exercise suggested a study of its rate of removal when introduced into the body from an outside source. Amounts of lactic acid, as sodium lactate, varying from 0.85 gm. to 2.1 gm. were injected intravenously into dogs. The rate of disappearance from the blood, and the changes in inorganic phosphates were studied. Within five to ten minutes after the injection as much as two-thirds of the lactic acid had disappeared from the blood. The concentration was 60 to 80 mg. per 100 cc. as contrasted with a possible 100 to 300 mg. had all the injected lactic acid remained in the blood and been evenly distributed. Thirty minutes after the injection the rate of removal of lactic acid became much slower. Normal values were obtained only after one to two hours. The first rapid decrease is undoubtedly due for the most part to a diffusion of lactic acid from the blood into other body fluids. The inorganic phosphates of the blood decreased after the injection, the decrease being greater the larger the amount of sodium lactate injected. The coincident disappearance of phosphates and lactic acid suggests the formation of the hexose phosphate, lactacidogen. Urine analyses indicate only negligible quantities of the injected lactic acid are excreted.

The experiments on the whole indicate that lactic acid injected into the blood disappears rapidly, being synthesised to lactacidogen and glycogen just as is the lactic acid produced as the result of body metabolism.

Studies in Serum Electrolytes. II. The Electrolyte Composition and the pH of Serum of a Poikilothermous Animal at Different Temperatures.—J. H. AUSTIN, F. W. SUNDERMAN and J. G. CAMACK (from the John Herr Musser Department of Research Medicine, University of Pennsylvania). It has been established in mammals that at constant body temperature there is a tendency for the reaction of the blood to be maintained constant. This implies constant hydrogen-ion concentration, constant hydroxyl-ion concentration and constant amount of base bound per gram of any give protein. When the temperature of an aqueous solution such as blood is changed it is impossible for both hydrogen-ion and hydroxyl-ion concentrations to remain constant. It seemed important to determine under conditions of changing body temperature what would be the adjustment of the hydrogen-ion and hydroxyl-ion concentrations of the blood, whether one would be kept constant and if so which one, or whether there exists some other more fundamental biological relation which determines the resulting reaction of the blood.

In this study it was thought desirable to investigate an animal in which marked changes of body temperature can be induced physiologically. Accordingly, an animal was sought among the reptilia. With the assistance of Dr. Herbert Fox and of Mr. C. Emerson Brown

Director of the Gardens of the Philadelphia Zoölogical Society, the alligator was selected as suitable for the purpose and five of these animals and the facilities of Dr. Fox's laboratory were placed at the disposal of the John Herr Musser Department of Research Medicine. These animals were kept for periods of three or more days in water at from 7° to 10° C. At the end of these periods the animals had cloacal temperatures of from 8.5° to 9.8° C. The same animals were kept for other periods of three or more days in water at from 35° to 39° C. At the end of these periods they had cloacal temperatures from 34.6° to 36.0° C.

The serum of these animals showed at the higher temperature, as compared with the lower, marked increase in concentration of glucose and lactic acid, slight increase of protein, phosphate and chloride, and a higher CO_2 tension; no change or perhaps a slight diminution in total base, but marked diminution in bicarbonate.

The answer to the question under investigation, it is believed, was found in the fact that the reaction of the serum at both temperatures was such as to maintain constant the base bound by protein. This involves considerable change in hydrogen-ion concentration ($\text{pH}_{9.0} = 7.72$; $\text{pH}_{35.0} = 7.27$); a less marked change in hydroxyl-ion concentration ($\text{pOH}_{9.0} = 6.73$; $\text{pOH}_{35.0} = 6.43$). That the change in reaction with temperature should be that necessary to keep constant the base bound by protein is probably necessary in order to keep undisturbed the osmotic relation between tissue cells and serum.

On the Postnatal Growth in the Area of the Optic Nerve in Albino and in Gray Norway Rats.—H. H. DONALDSON (from the Wistar Institute of the University of Pennsylvania).

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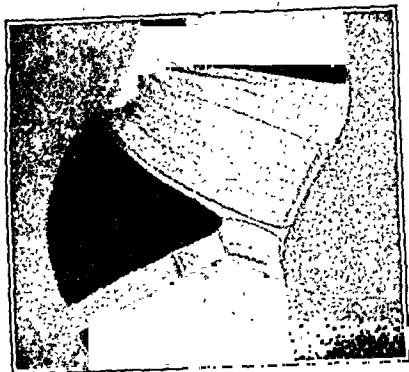
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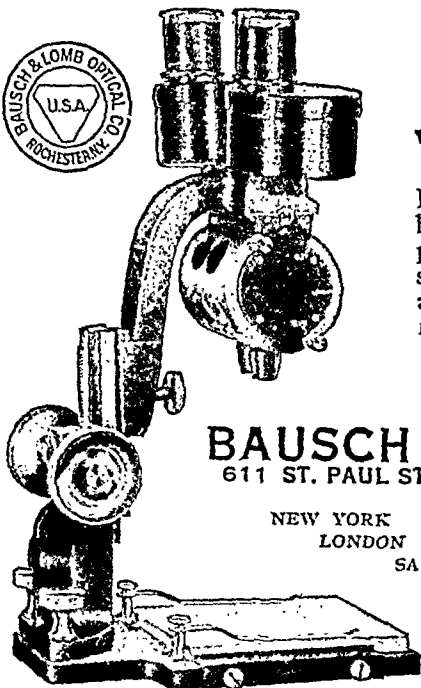
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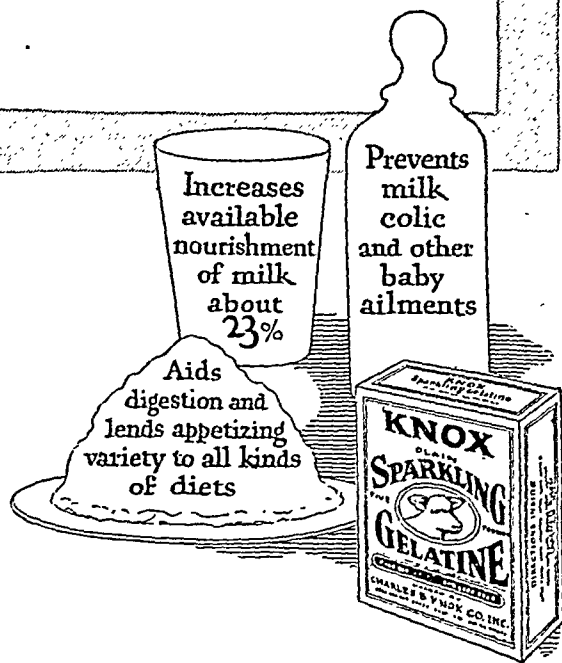
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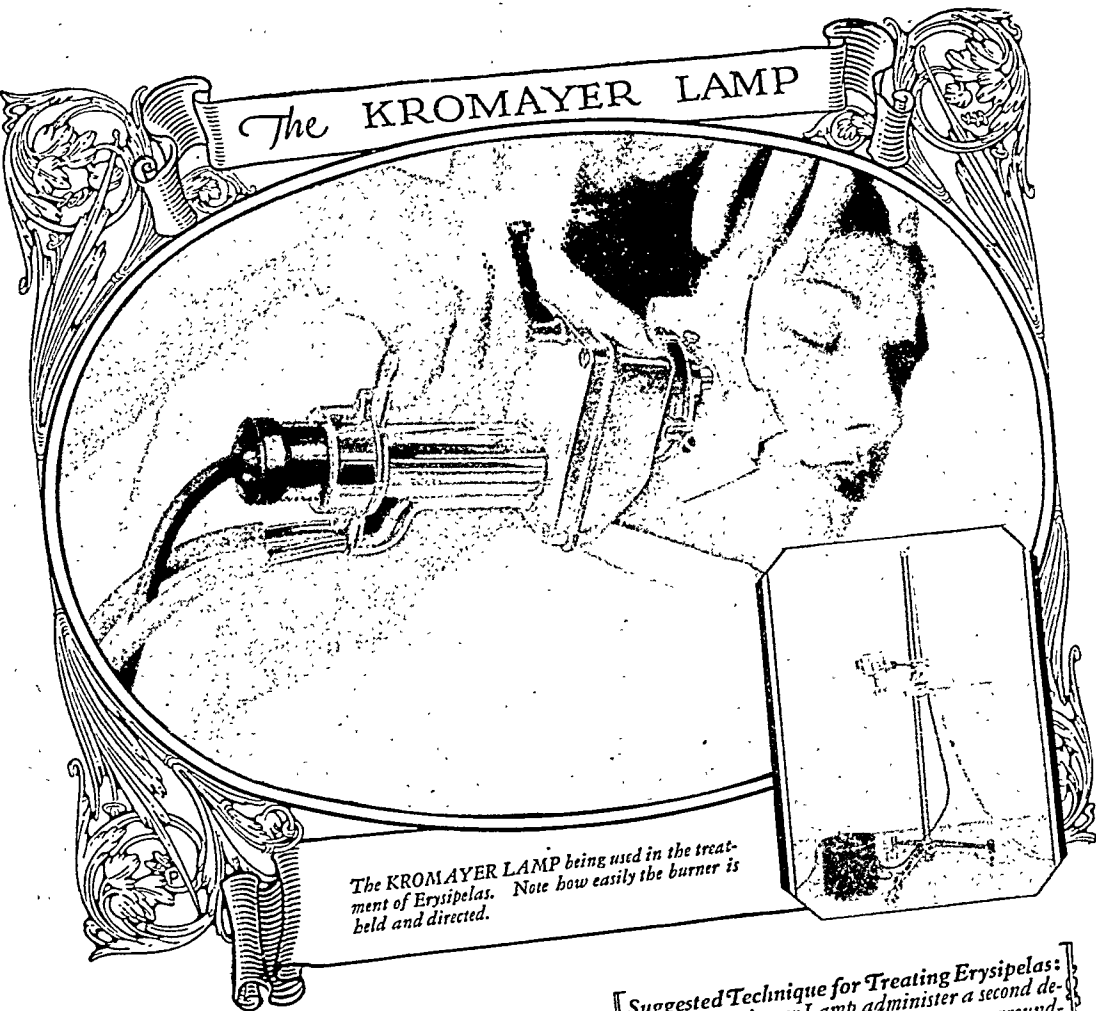
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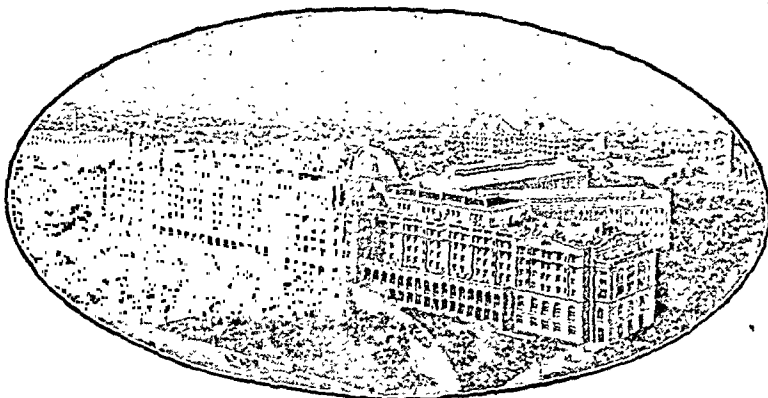
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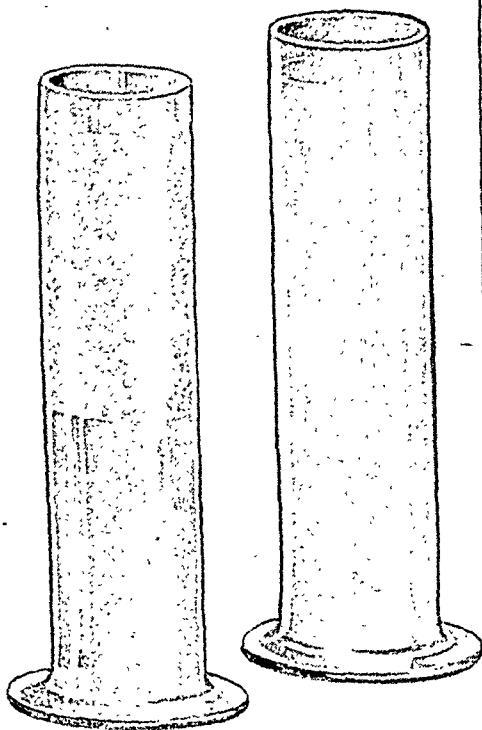
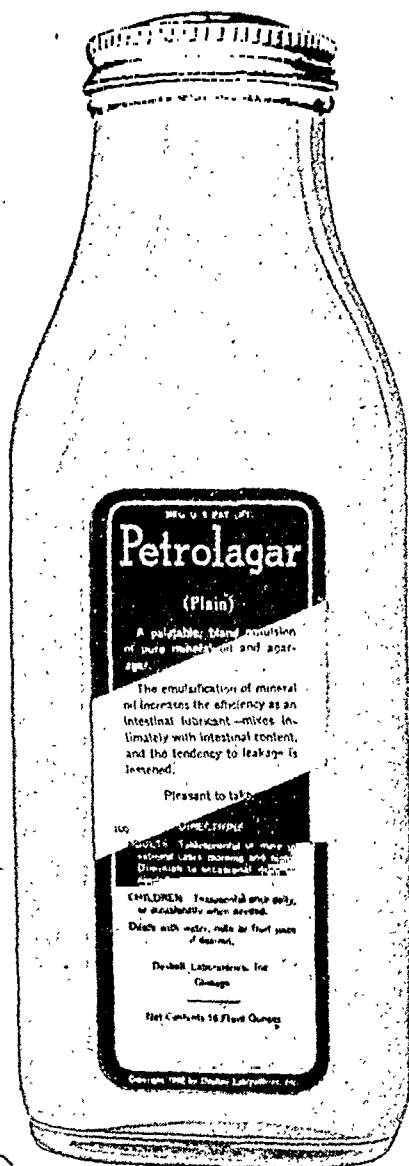
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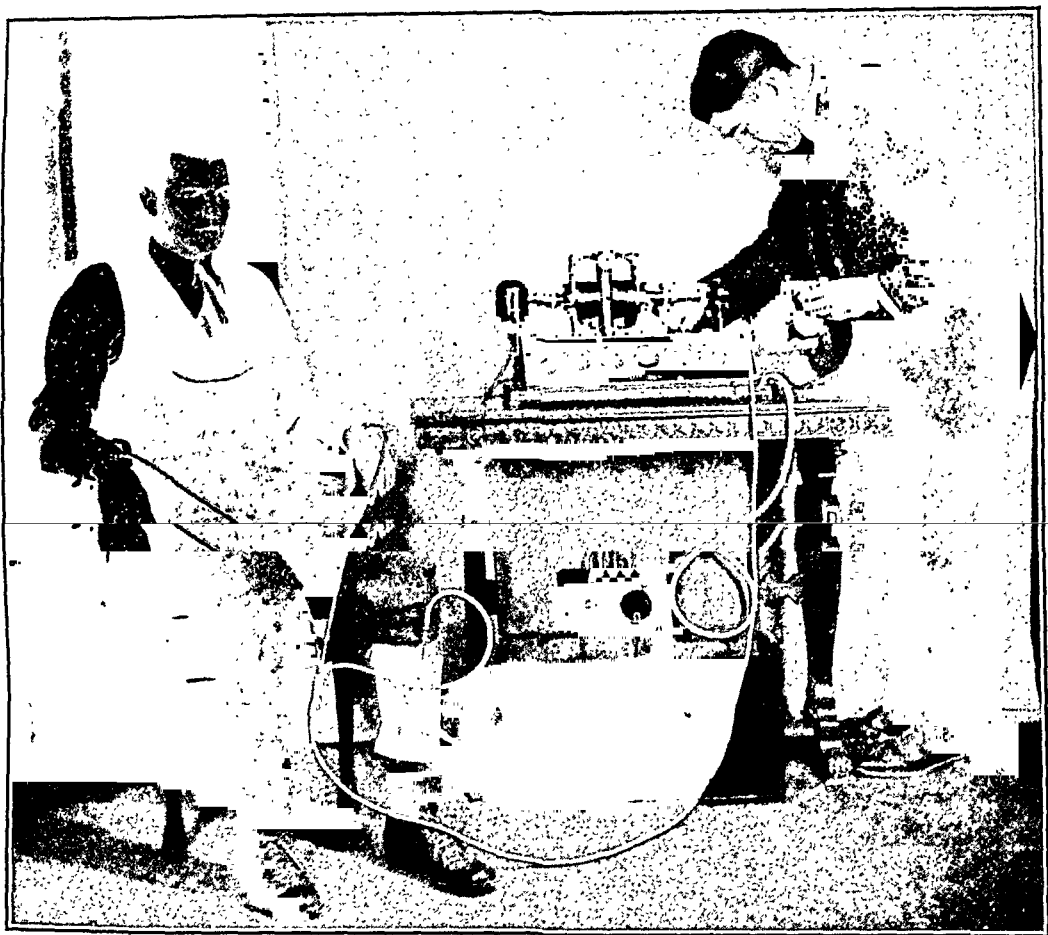
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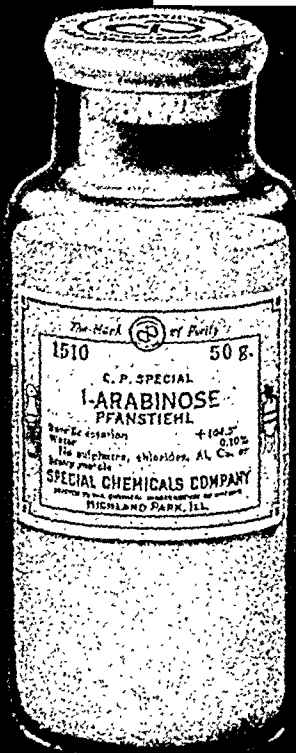
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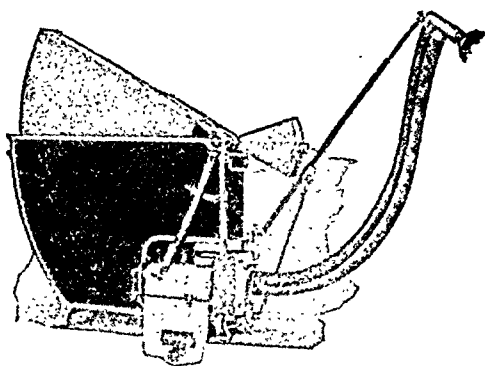
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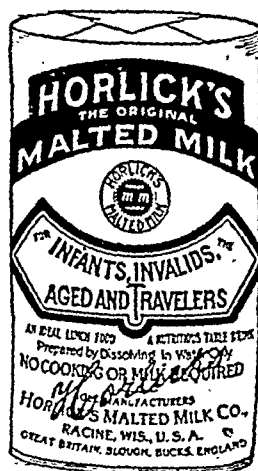
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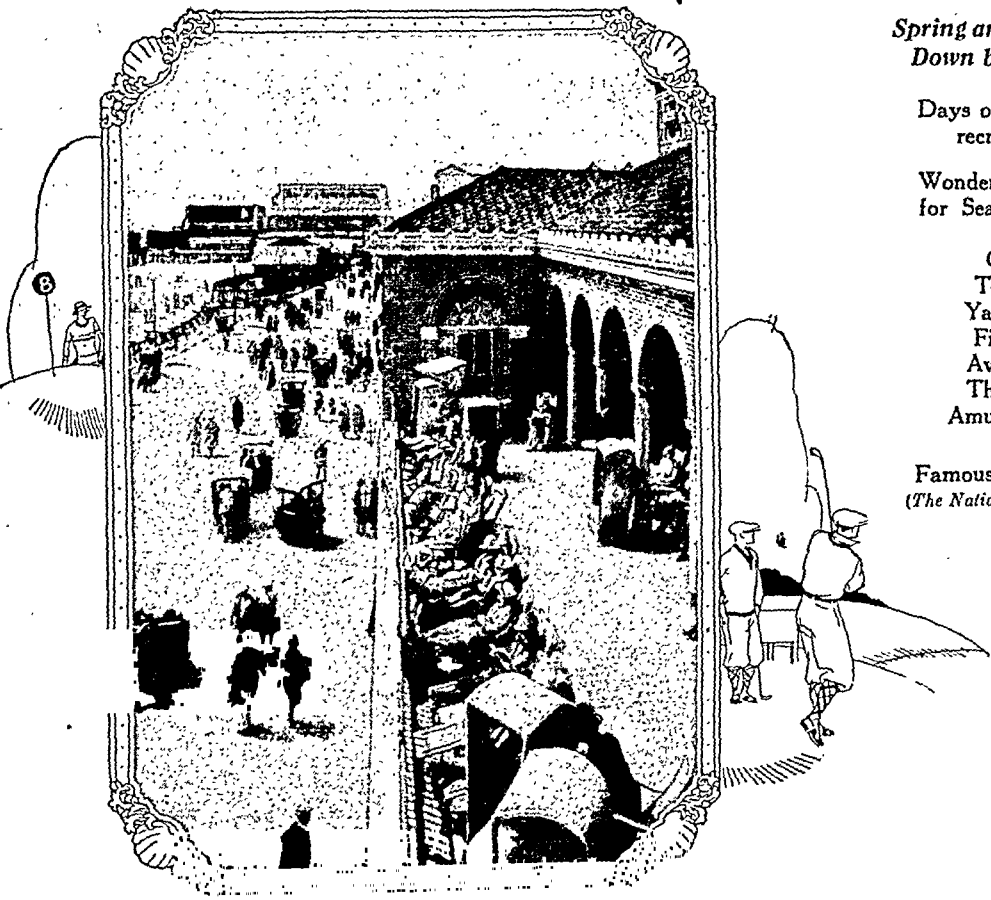
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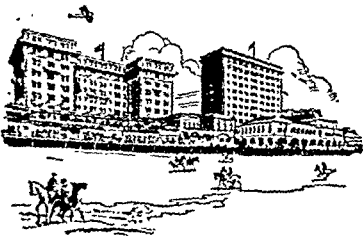
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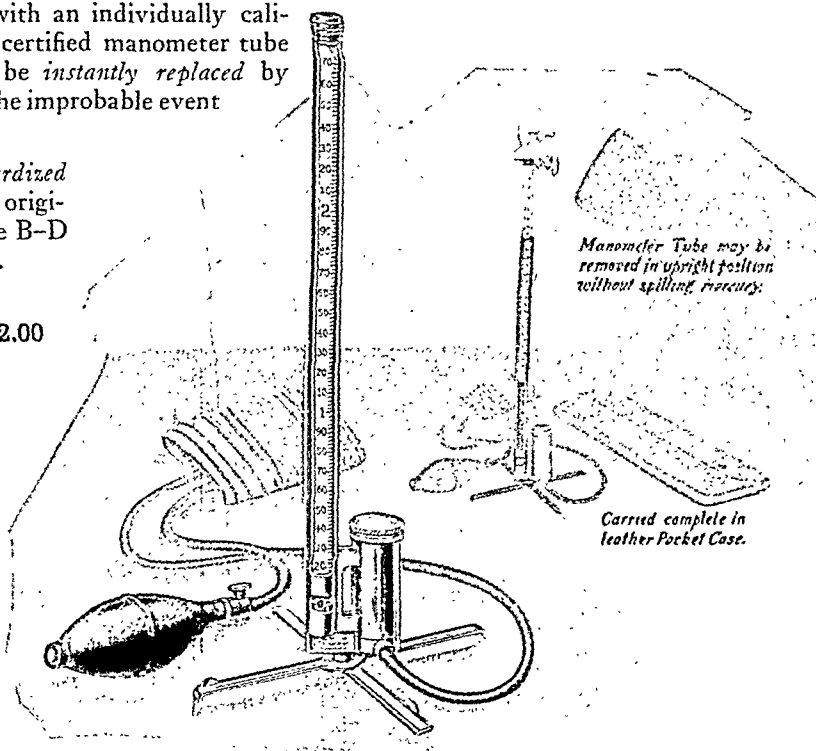
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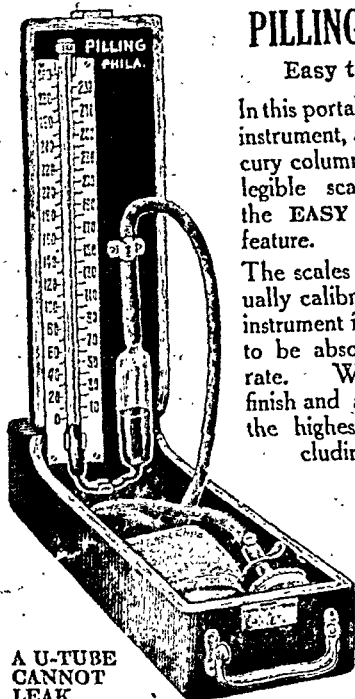
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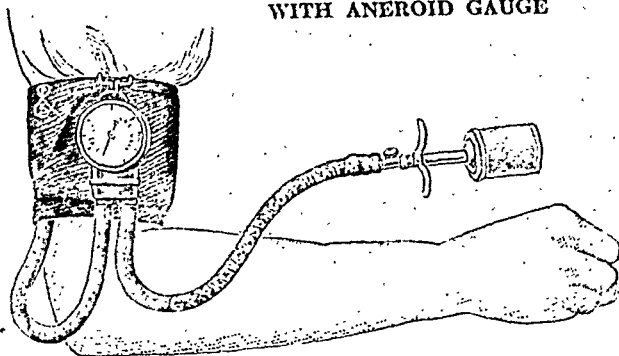


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THE fact that Mellin's Food is free from starch and relatively low in dextrins, are other matters for early consideration in attempting to overcome constipation caused from the use of modifiers containing starch or carbohydrate compounds having a high dextrins content.

THE fact that Mellin's Food modifications have a practically unlimited range of adjustment is also worthy of attention when constipation is caused by fat intolerance, or an excess of all food elements, or a daily intake of food far below normal requirements, for all such errors of diet are easily corrected by following the system of infant feeding that employs Mellin's Food as the milk modifier.

Physicians who are interested in this subject matter will find it presented in a rational manner in a pamphlet entitled "*Constipation in Infancy*", a copy of which will be mailed promptly upon request.

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DR. R. MCCARRISON (*ibid*) states that, "the absence of growth vitamins is capable of producing pathologic changes in the tract which frequently assume the clinical form of colitis. This observation is of the highest importance in view of the frequency with which this malady is encountered at the present day . . ."

DR. B. L. WYATT (*Chronic Arthritis and Fibrositis*, Wm. Wood & Co., 1933) says: "The frequency with which gastro-intestinal disturbances are encountered in arthritis patients points to the therapeutic importance of Vitamine B. This is particularly true in those cases which are characterized by bowel atonicity. Vitamine B may be most satisfactorily administered to such patients in the form of . . . Harris' yeast extract tablets."

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